



Automated pupillometry for the prediction of neurologic outcomes in children requiring extracorporeal membrane oxygenation (ECMO)

Molly McGetrick¹ · Nicolle Diaz² · Xilong Li³ · Tyler Terrill⁴ · Kari Powers⁵ · Rana Said⁴ · Deepa Sirsi⁴ · Lakshmi Raman² · Darryl Miles²

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Abstract

Neurologic injury is a significant cause of morbidity and mortality in pediatric extracorporeal membrane oxygenation (ECMO). Noninvasive neurologic monitoring is important for early detection and management of neurologic injury. Automated infrared pupillometry (AP) provides accurate and repeatable bedside quantitative measurements of pupil reactivity via the Neurological Pupil Index (NPi®). We evaluated if any abnormal NPi (defined as an NPi < 3) during the first 72 h of ECMO support could identify patients at risk for death or disability at discharge. An observational cohort of pediatric patients who required ECMO support was analyzed. NPis were measured during the first 72 h after ECMO cannulation using the NPi®-200 automated pupillometer, and the lowest value (NPi-min) was identified. The primary outcome was death prior to hospital discharge. The secondary outcome was discharge Functional Status Scale (FSS) score > 10, indicating at least moderate disability. A total of 75 patients were included in the study, of whom 26 (35%) died and 49 (65%) survived. Seventeen patients had an NPi-min < 3 during the first 72 h of their ECMO course. Patients who died had significantly lower median NPi-min values compared with patients who survived (2.6 vs. 4.3, $p = 0.0008$). An NPi-min < 3 was associated with increased mortality; in adjusted analysis, higher NPi-min was associated with lower odds of death (OR 0.57 per 0.5-unit increase, 95% CI 0.40–0.81, $p = 0.0015$); independent of age category (neonate versus non-neonate); ECMO type (venoarterial (VA), versus venovenous (VV)); electroencephalogram (EEG) severity; and pre-ECMO Pediatric Sequential Organ Failure Assessment (pSOFA) score. This model had a good discriminatory capacity for death with an area under the receiver operating curve (AUROC) of 0.82. In contrast, NPi-min was not significantly associated with at least moderate disability (FSS > 10) in adjusted analysis (OR 0.83 per 0.5-unit increase, 95% CI 0.60–1.15, $p = 0.26$; AUROC 0.70).

Conclusion: In children undergoing ECMO support, any NPi measurement of less than 3 during the first 72 h of ECMO initiation is associated with hospital mortality, but associations with at least moderate discharge disability are less clear. Automated pupillometry can be a useful tool for the early prognostication of pediatric patients requiring ECMO.

What is Known:

- Children supported on extracorporeal membrane oxygenation are at a disproportionately higher risk for death and neurological morbidity compared with the broader critically ill pediatric population.
- Automated pupillometry provides objective bedside assessment of pupillary reactivity, but its prognostic value in pediatric ECMO remains poorly defined.

What is New:

- In this single-center study of pediatric patients supported on extracorporeal membrane oxygenation, a minimum Neurological Pupil Index less than 3 within the first 72 hours of ECMO support was independently associated with in hospital mortality, but its association with discharge functional disability was less consistent.

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Molly McGetrick and Nicolle Diaz have contributed equally to this work.

Extended author information available on the last page of the article

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Background

Extracorporeal membrane oxygenation (ECMO) is an advanced form of cardiorespiratory support increasing in use in children with refractory cardiopulmonary failure [1]. While ECMO has improved overall mortality rates from critical illness, up to one-third of patients suffer acute neurological injury while on ECMO (15–36%), a figure that likely underestimates the burden of occult brain injury identified on neuroimaging studies obtained after ECMO support [2],[3]. Early identification of neurologic complications while on ECMO support and timely interventions are essential to improve neurological outcomes in this vulnerable population [4].

In the modern critical care setting, multimodal neurological monitoring plays an essential role in identifying brain injury in high-risk patient populations, such as those supported on ECMO. Guidelines describing optimal care for neonates and children on ECMO endorse routine structured neurological monitoring, including serial bedside neurological exams, cerebral oximetry, continuous electroencephalography (EEG), and neurological imaging in response to acute neurological changes and after ECMO discontinuation [5],[6]. The automated pupillometer (AP) is a newer modality showing promise as an adjunct neuromonitoring tool and prognostic biomarker in critical illness. This device offers advantages over the standard subjective pupillary assessments. AP is non-invasive, requires minimal training to implement, and provides rapid objective assessment of pupillary dynamics with high accuracy and reliability [7],[8]. The Neurological Pupil Index (NPi®), a unitless marker of reactivity derived from integrating multiple variables of pupillary dynamics from normative data in adults, is the most widely studied and clinically utilized variable produced by AP [9]. In adult studies, NPi has demonstrated good prognostic performance for neurological injury and functional outcomes following acute brain injury, cardiac arrest, and VA-ECMO [9],[10],[11],[12]. As a result, AP is becoming increasingly adopted in many adult neurocritical care units [13]. While fewer studies in pediatrics have been published, there are data to support that low NPi values may be associated with high intracranial pressure in traumatic brain injury and adverse neurological outcomes in critically ill children [14],[15]. To our knowledge, the role of NPi as a prognostic outcome biomarker in pediatric ECMO patients has not yet been described,

despite the unique vulnerability to neurologic injury in this population.

The objective of this study was to evaluate the association between the presence of any NPi value (NPi-min) less than 3 within the first 72 h of ECMO support and unfavorable outcomes, including (1) death prior to hospital discharge, and (2) a discharge functional status scale (FSS) score of ≥ 10 , indicating at least moderate disability. We hypothesized that patients with an NPi-min < 3 during the first 72 h of ECMO would experience worse outcomes compared to those with measured NPi-min values ≥ 3 during this period.

Methods

Study design and patient selection

We conducted a retrospective, single-center observational study of patients less than 18 years of age admitted to the pediatric or cardiovascular intensive care unit at Children's Medical Center (Dallas, TX) between August 2020 and November 2022 who required ECMO support. The study was approved by the University of Texas Southwestern Institutional Review Board (STU-2019-1424; automated pupillometry in pediatric patients, approved 12/1/21, and conducted in accordance with the ethical standards of the Committee for the Protection of Human Subjects. A waiver of informed consent was granted given the non-interventional nature of this study. Patients were included if they were cannulated onto ECMO within the study period and had more than one pupillometry measurement documented in the electronic medical record within the first 72 h after cannulation. Exclusion criteria included a duration of ECMO support less than 24 h, exposure to volatile anesthetics during pupillary measurements and presence of any ocular pathology that would alter feasibility and reliability of a pupillary assessment, such as trauma, recent surgery of the orbit, and diseases affecting the globe or optic nerve.

Demographic and clinical variables

Demographic and clinical variables were extracted from the electronic health record (EHR) system (Epic Systems, Verona, WI), shown in Table 1. Baseline clinical data included age at ECMO cannulation, sex, intensive care unit (ICU) location (pediatric versus cardiac ICU), ECMO type (VA versus VV), primary ECMO indication (cardiac versus respiratory), and whether the patient required continuous renal replacement therapy (CRRT) while on ECMO. Given the unique neurodevelopmental differences between neonates and older children, the population was

Table 1 Patient characteristics stratified by lowest Neurologic Pupillary Index (NPi)

Patient characteristic	Overall (<i>n</i> = 75)	NPi-min < 3 (<i>n</i> = 17)	NPi-min ≥ 3 (<i>n</i> = 58)	<i>p</i> value
Age (months), median (IQR)	24 (0, 146)	70 (0, 168)	16 (0, 138)	0.256
Neonate, <i>n</i> (%)	23 (30.7)	5 (29.4)	18 (31)	0.898
Non-neonate	52 (69.3)	12 (17.6)	40 (69)	
Female gender, <i>n</i> (%)	43 (57.3)	11 (64.7)	32 (55.1)	0.485
ECMO location, <i>n</i> (%)				0.605
PICU	49 (65.3)	12 (70.6)	37 (63.8)	
CICU	26 (34.7)	5 (29.4)	21 (36.2)	
ECMO type, <i>n</i> (%)				0.334
VA ECMO	60 (80)	15 (88.2)	45 (77.6)	
VV ECMO	15 (20)	2 (11.7)	13 (22.4)	
ECMO indication, <i>n</i> (%)				0.532
Cardiac	42 (56)	13 (76.5)	29 (50)	
Respiratory	33 (44)	4 (23.5)	29 (50)	
ECMO duration (days), median (IQR)	5.1 (3.8, 12)	4.3 (3.4, 17.5)	5.3 (3.9, 11.7)	0.584
pSOFA on cannulation, median (IQR)	13 (11, 15)	14 (13, 15)	13 (11, 15)	0.139
Had EEG, <i>n</i> (%)	66 (88)	15 (88.2)	51 (88)	0.973
EEG score, <i>n</i> (%) [*]				0.006
Severe	13 (19.7)	7 (46.7)	6 (11.8)	
Moderate	35 (53)	7 (46.7)	28 (54.9)	
Mild	18 (27.3)	1 (6.7)	17 (33.3)	
Had neuroimaging, <i>n</i> (%)	54 (72)	10 (58.8)	44 (75.9)	0.169
Had CRRT, <i>n</i> (%)	28 (37.3)	8 (47.1)	20	0.4
ICU LOS (days), median (IQR)	29.9 (12.9, 53)	19.6 (4.6, 39.3)	33.4 (17, 53)	0.07
Hospital LOS (days), median (IQR)	41.8 (17, 67.5)	19.6 (5.3, 39.3)	44.5 (26.8, 79)	0.006
death, <i>n</i> (%)	26 (34.7)	15 (88.2)	11 (19)	<0.001
Discharge FSS ≥ 10	50 (66.7)	16 (94.1)	34 (58.6)	0.006
Neurologic cause of death, <i>n</i> (%)	9/26 (34.6)	7/15 (46.7)	2/11 (18.2)	0.131

Baseline demographic and clinical characteristics of the study cohort stratified by the occurrence of a minimum Neurologic Pupillary Index of (NPi < 3 vs. > 3) within the first 72 h of ECMO. *p* values are comparing the 2 subgroups (any NPi < 3 versus all NPi ≥ 3). The asterisk “*” represents *n* (%) of those monitored with EEG

Abbreviations: NPi Neurologic Pupillary Index, NPi-min minimum Neurologic Pupillary Index measurement, IQR interquartile range, ECMO extracorporeal membrane oxygenation, PICU pediatric intensive care unit, CICU cardiac intensive care unit, VA venoarterial, VV venovenous, pSOFA pediatric sequential organ function, EEG electroencephalogram, CRRT continuous renal replacement therapy, LOS length of stay, FSS functional status scale

subclassified into neonates (patients who were cannulated onto ECMO between 0 and 30 days of life) and non-neonates. The Pediatric Sequential Organ Failure Assessment (pSOFA) score, a validated tool which assesses risk of mortality using age-adjusted cutoffs for cardiovascular, respiratory, renal, hepatic, neurologic, and coagulation function, was calculated for each patient prior to ECMO cannulation [16].

Per our institutional protocol, all patients were placed on continuous EEG monitoring (Natus Neuroworks, Natus Medical Incorporated, Pleasanton, CA) for a minimum of 24 h after ECMO cannulation. If significant EEG abnormalities were present, including seizures, asymmetry, or moderate to severe background EEG abnormalities such as low voltage or diffuse non-reactive slowing, the monitoring

period was extended at the discretion of the treating medical team and epileptologist. EEG studies were reviewed by a board-certified pediatric epileptologist, who classified the EEG background pattern as mild, moderate, or severe, following established neonatal and pediatric scoring systems [17]. For analysis, EEG findings were dichotomized as severe versus non-severe (mild or moderate).

Automated pupillometry

Following our institutional protocol, all patients who were supported on ECMO received pupillometry using the NPi-200 pupillometer (NeuroOptics, Laguna Hills, CA, USA) in conjunction with standard neurological examinations. Each NPi-200 was outfitted with a patient-specific SmartGuard

which utilizes smart-card technology to store serial time-stamped pupillometry data. While nurses reported measurements in the EHR, data from the SmartGuard was used in our analysis. The clinical team was not blinded to the measurements, and although no standardized interventions were defined for specific NPi changes, these findings could prompt further diagnostic evaluation or therapeutic intervention if indicated. Measurements were suggested to be performed every 6–8 h for the first 72 h after ECMO cannulation at the medical team's discretion, with increased frequency if concerning clinical neurological exam findings or NPi trends were observed.

The NPi-200 pupillometer measures multiple dynamic components of the pupillary light reflex. For this study, pupillary size in millimeters (mm) was analyzed to identify anisocoria, defined as a > 1 mm inter-eye difference, along with the NPi, which ranges from 0 (non-reactive) to 4.9, with higher values indicating greater reactivity. The NPi is generated by a proprietary algorithm that quantifies the normality of the pupillary light reflex by integrating pupil size, latency, constriction velocity, and dilation velocity into a single unitless value [18]. For each patient, NPi measurements were pooled and analyzed collectively from both eyes. We recorded the minimum NPi value observed across all recorded measurements (NPi-min) within the first 72 h of ECMO support. Consistent with prior literature, we defined normal pupillary reactivity as an NPi-min ≥ 3 and abnormal reactivity as an NPi-min < 3 [19],[20].

Outcomes

For each patient, we collected duration of ECMO support and length of ICU and hospital stays. Our primary outcome was death prior to hospital discharge. Causes of death were categorized as non-neurologic when primarily due to extracerebral factors, such as refractory shock or multiorgan failure, and neurologic when death resulted from severe cerebral injury leading to brain death or withdrawal of life-sustaining therapies. Functional outcome after critical illness was assessed using the Functional Status Score (FSS) score, which is validated in pediatrics [21]. The FSS quantifies functioning in six discrete domains: mental status, sensory function, communication, motor, feeding, and respiratory status. Each domain is scored between 1 (normal) and 5 (very severe dysfunction), and the total score is the sum of all domains. The discharge FSS score was scored for each patient at the time of discharge from the ICU per institutional practice. A total score of 6–9 indicates normal function to mild dysfunction; FSS 10–15 indicates moderate dysfunction, and scores of 16 or greater indicate severe dysfunction. By convention, all patients who died were assigned

an FSS of 30. Prior work from our institution demonstrated excellent interrater reliability for FSS scoring [15].

Statistical analysis

Patients were stratified into two groups based on pupillometry findings during the first 72 h following ECMO cannulation: (1) those with an NPi-min < 3 and (2) those with an NPi-min ≥ 3 . Descriptive statistics were performed for all variables, with continuous variables expressed as median (interquartile range, IQR) and categorical variables expressed as a proportion (percentage). Univariate comparisons were performed with Fisher exact test for categorical variables and Wilcoxon test for continuous variables. Multivariable logistic regression was performed to assess the independent association between NPi and outcomes. pSOFA and NPi-min were modeled as continuous variables, scaled per 1-point increase, and 0.5-unit decrease, respectively, to enhance clinical interpretability. Covariates were selected based upon their biologic plausibility to influence outcomes. These included age categories (neonate versus non-neonate), ECMO type, EEG severity category (severe versus non-severe), and total pSOFA score. Model estimates are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Discrimination was assessed using the area under the receiver operating characteristic curve (AUROC). Optimal NPi-min thresholds for outcome discrimination were identified using Youden's index (J), defined as sensitivity + specificity – 1. The cutoff maximizing Youden's index on receiver operating characteristic (ROC) analysis was selected as the optimal threshold. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$.

Results

Patient and clinical characteristics

During the study period, 124 patients were supported on ECMO at our institution. Forty-seven patients were excluded because pupillometry data were not available during the study period, and 2 patients receiving sevoflurane were excluded due to the pupillary effects of this medication. Seventy-five patients were included, yielding an enrollment rate of 60%. The median age at ECMO cannulation was 24 months (interquartile range (IQR), 0–146), and 23 patients (31%) were neonates (Table 1). Forty-nine patients (65%) were admitted to the PICU, and 60 (80%) children required VA ECMO support. Sixty-three patients had an EEG within 72 h of ECMO cannulation, and 28 received CRRT while on ECMO.

Pupillometry measurements

Seventeen patients (23%) had an NPi-min < 3 in the first 72 h of ECMO support and 11 patients (14%) had at least one episode of anisocoria. Five patients had an NPi-min = 0, all of whom died. Four of the five of the patients with NPi-min = 0 had a neurological cause of death, while one patient died from irreversible multiorgan dysfunction. There were no statistically significant differences in age, sex, ICU location, ECMO type, ECMO indication, duration of ECMO support, or baseline pSOFA score among patients with an NPi-min < 3 and those with an NPi-min ≥ 3 (Table 1). EEG data was available for 63 patients (81.8%), and severe EEG scores were associated with an NPi-min < 3 ($p = 0.007$) as shown in Table 2. While patients with NPi-min < 3 had shorter lengths of stay (17 versus 45 days, $p = 0.003$), only 2 patients in the NPi-min < 3 group survived to hospital discharge indicating that timing of death in the most severe patients likely skewed this result.

The median NPi-min for patients who died was lower compared to patients who survived (2.6 versus 4.3,

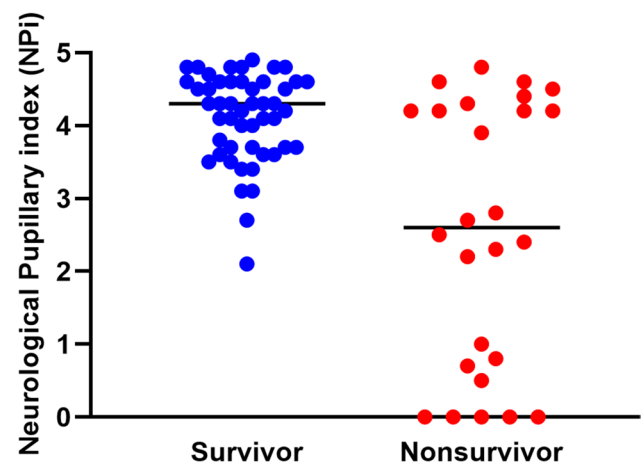


Fig. 1 Scatter plot of minimum Neurologic Pupil Index (NPi-min) values within the first 72 h after extracorporeal membrane oxygenation (ECMO) cannulation, stratified by survival status. Each point represents an individual patient. Horizontal lines indicate median values for each group. Nonsurvivors had significantly lower NPi-min values compared to survivors, and all patients with an NPi-min of 0 were non-survivors

Table 2 Clinical characteristics stratified by mortality status

Variable	All (n = 75)	Survived (n = 49)	Died (n = 26)	p value
Age, months, med [IQR]	24 [0–146]	8 [0–89]	87 [0–182]	0.034
Neonate, n (%)	23 (30.7)	16 (32.7)	7 (26.9)	0.609
Non-neonate				
Female, n (%)	43 (57.3)	29 (59.2)	14 (53.9)	0.656
Location, n (%)				0.305
PICU	49 (65.3)	30 (61.2)	19 (73.1)	
CICU	26 (34.7)	19 (38.8)	7 (26.9)	
ECMO type, n (%)				0.182
VA	60 (80)	37 (75.5)	23 (88.5)	
VV	15 (20)	12 (24.5)	3 (11.5)	
Reason for ECMO, n (%)				0.233
Cardiac	42 (56)	25 (51)	17 (65.4)	
Respiratory	33 (44)	24 (49)	9 (34.6)	
ECMO duration (days), med [IQR]	5.1 [3.8–11.9]	4.9 [3.8–9]	6.9 [4.2–17.5]	0.110
pSOFA score, med [IQR]	13 [11–15]	13 [11–15]	13.5 [11–15]	0.871
Had EEG, n (%)	66 (88)	42 (85.7)	24 (92.3)	0.403
EEG score, n (%)*				0.194
Severe	13 (19.7)	6 (14.3)	7 (29.2)	
Moderate	35 (53)	22 (52.4)	13 (54.2)	
Mild	18 (27.3)	14 (33.3)	4 (16.7)	
Had neuroimaging, n (%)	54 (72)	40 (81.6)	14 (53.9)	0.011
Had CRRT, n (%)	28 (37.3)	17 (34.7)	11 (42.3)	0.79
ICU LOS (days), med [IQR]	29.9 [12.9–53]	39 [23.6–55.8]	16.9 [5.3–39.4]	0.002
Hospital LOS (days), med [IQR]	41.8 [17–67.5]	51.6 [37.3–82.6]	18.3 [5.3–40.3]	<0.001

Comparison of baseline characteristics between survivors and non-survivors

Abbreviations: *IQR* interquartile range, *PICU* pediatric intensive care unit, *CICU* cardiac intensive care unit, *ECMO* extracorporeal membrane oxygenation, *VA* venoarterial, *VV* venovenous, *pSOFA* pediatric sequential organ function, *EEG* electroencephalogram, *CRRT* continuous renal replacement therapy, *LOS* length of stay

$p=0.0008$; Fig. 1). Median NP_i-min was lower for patients with at least moderate disability compared to those without (3.5 versus 4.0, $p=0.65$), but the difference was not significant.

Patient outcomes

In total, 26 (35%) patients died during the study period. A comparison of clinical features based upon mortality outcome is shown in Table 2. Mortality did not differ significantly between neonates and non-neonates (30.4% vs 36.5%, $p=0.80$). Of the 49 survivors, 16 patients (21% of total cohort) had no to mild disability based on an FSS score of 6–9 at discharge, and 33 patients (44% of total cohort) survived with at least moderate disability (discharge FSS score ≥ 10). Among non-survivors, neurological injury was identified as the cause of death in 9/26 (35%). Neurological causes of death included severe global hypoxic ischemic brain injury in 6 patients and massive intracranial hemorrhage in 3 patients. Non-neurologic causes of death were as follows: multiorgan failure [8], cardiac failure, not amenable to transition to durable mechanical circulatory support or transplant [5], pulmonary hypertension [2], hemorrhagic shock [1], and irreversible respiratory failure [1].

An NP_i-min < 3 was observed in 15/26 (58%) patients who died, compared with 2/49 (4%) who survived. Among patients with an NP_i-min < 3 , 15/17 (88%) died, while 2/17 (12%) survived, including one with mild disability (discharge FSS 8) and one with moderate disability (FSS 12). Comparatively, 48/58 (83%) of patients with an NP_i-min > 3 survived. The presence of an NP_i-min < 3 occurred in 7/9 (78%) patients with neurological cause of death compared to 8/17 (47%) with non-neurological causes of death. Of the patients with a neurological cause of death and NP_i-min > 3 , one patient suffered an acute intracranial hemorrhage 9 days into ECMO support while the other showed progressive evidence of anoxic brain injury during ECMO.

Prognostic performance of NP_i for death and functional status

Multivariable logistic regression analyses were performed to evaluate the association between NP_i-min and outcomes, including mortality (Table 3) and at least moderate disability. In an adjusted logistic regression model, higher NP_i-min was independently associated with lower odds of mortality (OR 0.57 per 0.5-unit increase, 95% CI 0.40–0.80, $p=0.0015$), after adjustment for age category, ECMO type, EEG severity, and illness severity (pSOFA score). Using this model, each 0.5-unit increase in NP_i-min was associated with a 44% reduction in the odds of mortality. No other

Table 3 Multivariable regression analysis of mortality

Variable	Adjusted odds ratio	95% confidence interval	<i>p</i> value
Neonate (vs non-neonate)	0.749	0.27–3.32	0.70
VA ECMO (vs VV)	8.091	0.77–84.74	0.08
Severe EEG (vs non-severe)	1.51	0.32–7.18	0.60
Total pSOFA score (per point increase)	0.864	0.7–1.08	0.19
Minimum NP _i (per 0.5 unit decrease)	0.57	0.4–0.81	0.002

Multivariable model adjusted a priori for age category, ECMO type, illness severity (pSOFA), and EEG severity. Model discrimination: AUROC=0.82. Adjusted odds ratios for continuous variables are reported per unit change. For total pSOFA score, the odds ratio reflects the change in odds of mortality per 1-point increase in pSOFA score. For minimum NP_i, the odds ratio reflects the change in odds of mortality per 0.5-point decrease in NP_i

Abbreviations: ECMO, extracorporeal membrane oxygenation, VA, venoarterial, VV, venovenous, pSOFA, pediatric sequential organ failure assessment, NP_i, neurologic pupillary index, pSOFA, pediatric sequential organ failure assessment, VA, venoarterial, VV, venovenous

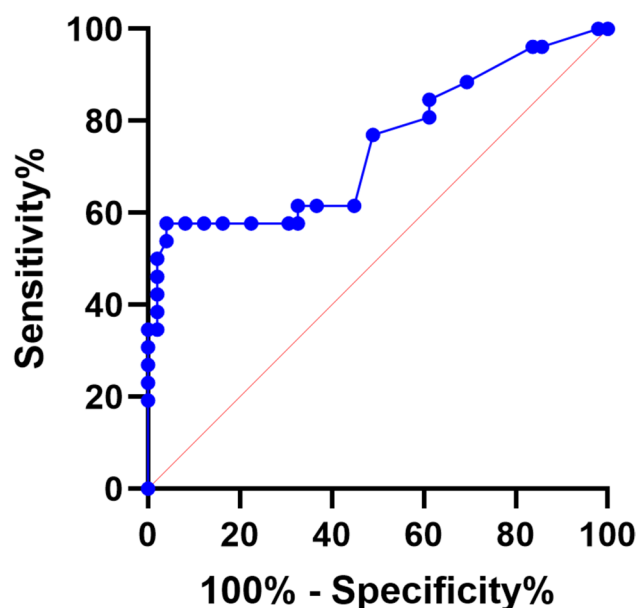


Fig. 2 Receiver operating characteristic (ROC) curve demonstrating the performance of minimum Neurologic Pupil Index (NP_i-min) in predicting mortality among pediatric patients supported with extracorporeal membrane oxygenation (ECMO), adjusted for age category (neonate vs. non-neonate), ECMO type (VA vs. VV), electroencephalogram (EEG) severity, and illness severity (pSOFA score). The model demonstrated good discriminative ability, with an area under the receiver operating characteristic curve (AUROC) of 0.82. Sensitivity is plotted against 1–specificity across predicted probabilities of mortality

covariates were associated with mortality including neonate versus non-neonate (OR 0.75, 95% CI 0.17–3.30; $p=0.7$); VA versus VV ECMO (8.09, 95% CI 0.77–84.70; $p=0.08$); severe versus mild-moderate EEG score (OR 1.51, 95% CI 0.32–7.18; $p=0.6$); and total pSOFA score (OR 0.86, 95% CI 0.70–1.07; $p=0.19$). The AUROC for this model demonstrated good discriminative capacity at 0.82 (Fig. 2). Using Youden- J statistics, the NP_i-min that best predicted mortality was 2.8, corresponding to a sensitivity of 57% and specificity of 96% (PPV 88%, NPV 81%). In contrast to the mortality model, NP_i-min was not significantly associated with at least moderate functional impairment in adjusted analysis (OR 0.83 per 0.5-unit increase, 95% CI 0.60–1.15, $p=0.26$; AUROC 0.70).

Discussion

This study demonstrates that pupillary abnormalities identified by minimum NP_i within the first 72 h of ECMO cannulation are significantly associated with in-hospital mortality. To our knowledge, this relationship has not been described previously in this population, thereby addressing an important gap in the existing literature. These findings support the potential role of automated pupillometry as an early, objective bedside biomarker for risk stratification and neuroprognostication in critically ill children requiring ECMO.

While NP_i has been described in adults supported on ECMO, data on its use as a biomarker in pediatric ECMO remain limited. Using the same cutoff value of an NP_i < 3 to define abnormal reactivity, Miroz et al. determined that any abnormal NP_i between days 1 and 3 of ECMO support was 100% specific for mortality [12]. Furthermore, a positive pupillary response after extracorporeal cardiopulmonary resuscitation (ECPR) was correlated with a favorable neurological outcome in an adult cohort [22]. Given that mortality rates for patients requiring ECMO (35% in our cohort) far exceed those in the general PICU population, which is reported around 2%, there exists a need for reliable bedside biomarkers which predict injury and death in this exceedingly vulnerable population [23]. There are few studies which examine the use of NP_i in critically-ill children. Lower NP_i has been associated with intracranial hypertension in brain-injured patients with intracranial pressure monitoring, poor functional outcomes after brain injury, and other forms of critical illness [14],[15],[24].

In our cohort, we found that an NP_i ≤ 2.8 on the univariate model was highly specific for mortality. This contrasts other pediatric studies which revealed optimal cutoff values for mortality of NP_i ≤ 0.5 in children with various forms of neurological injury and NP_i ≤ 1.5 for a more heterogeneous population of critically ill children [15],[24]. This discrepancy may reflect our timeframe of data collection (the first

72 h of ECMO) and the unique physiologic context of children who require ECMO support and may suggest that NP_i changes are more sensitive to brain dysfunction in this population compared to others. Children supported by ECMO often have limited physiologic reserve and are at increased risk of impaired cerebral perfusion and perturbations in cerebral hemodynamics, which can lead to morbid brain injury. While our threshold demonstrated high specificity, sensitivity was 58%. This suggests that while abnormal NP_i values are strongly associated with mortality on ECMO, NP_i should not be used in isolation to exclude adverse outcomes.

Although NP_i-min demonstrated a strong association with mortality, its discrimination for at least moderate functional impairment (discharge FSS > 10) was limited. Given the relatively small sample size, we did not establish an optimal NP_i-min threshold for functional outcomes. In contrast, prior studies in pediatric brain injury cohorts have identified thresholds, including NP_i < 3.1 for predicting FSS > 12 and NP_i < 3.5 for unfavorable outcomes defined by a Pediatric Overall Performance Category score > 3 [24]. Similarly, adult studies have reported that any NP_i ≤ 2 within 72 h of cardiac arrest was 100% specific for unfavorable outcomes, and that any NP_i ≤ 2.8 after large hemispheric ischemic stroke was associated with neurological deterioration from cerebral edema [10],[11]. Although these thresholds can help conceptualize the prognostic potential of using NP_i, outcomes associations may also be dependent on multiple factors including non-neurologic causes of death or morbidity, mechanism of injury, and timing of the assessments. Larger studies among specific populations would be needed to validate these values before integration into prognostic models.

While our study numbers were small, the fact that all patients who had an NP_i=0 died is not unexpected. This suggests that using AP, as a marker of pupillary non-reactivity, can be a highly specific marker for poor neurologic prognosis. In larger adult cohorts, any NP_i=0 has shown to be 100% specific for death or poor neurological outcomes after cardiac arrest [12],[19],[20]. While pupillary measurements may be confounded by hemodynamic parameters, sedation, and neuromuscular blockade, complete absence of pupillary reactivity suggests severe midbrain dysfunction which might occur secondary to brainstem anoxia, such as after cardiac arrest, or compression from edema or intracranial hemorrhage. Our study can serve as a basis for future research in determination of specific NP_i values threshold above zero early in the ECMO period that are both specific and sensitive for outcome prediction.

About one-third of the patients in this cohort were neonates, a population known to have differences in pupillary development and physiologic responses compared with older children [25]. Compared with older children, neonates have smaller pupils and less well-defined pupillary margins, which may reduce the accuracy of automated edge detection by the infrared camera of the pupillometer [26].

Additionally, behavioral variability, particularly inconsistent patient cooperation, may compromise measurement accuracy. While there is limited published normative pediatric pupillary data, age-related changes in pupillary dynamics should be considered when assuming normative distributions [25],[27]. Theoretically, age may have impacted the distribution of values and prognostic performance of our models, yet there were no differences between neonates and non-neonates in terms of proportion of patients with NP_i-min < 3 and univariate associations with outcome, suggesting this tool may have clinical applicability for prognostication in all ages.

Offering additional evidence that the NP_i can accurately reflect ongoing brain dysfunction, we also observed a significant association between severe EEG scores and NP_i-min < 3. Abnormalities in EEG voltage, asymmetry, non-reactive slow background activity disproportionate to sedative medications, and electrographic seizures are well-established markers of cerebral dysfunction which have been associated with adverse outcomes in pediatric ECMO [17],[28]. While EEG primarily reflects cortical activity, the pupillary light reflex is thought to be mediated primarily in the brainstem. However, it is known that the pupillary light reflex can also be influenced by cortical pathways in a complex system. It is unclear how the NP_i is related to changes in EEG findings. It may be that disruptions in both neurological regions can occur simultaneously with global brain dysfunction, or alternatively it may be possible that changes in the NP_i may be reflecting disruptions in cortical-brainstem interactions on ECMO.

Our study has several limitations worth mentioning. This was a single-center observational study which included a heterogeneous population with respect to underlying disease processes, type of ECMO support, and age. Therefore, larger multicenter studies would be needed to confirm if our findings are widely generalizable. Because this tool was already in use in our ICU, clinicians were not blinded to the results of the pupillometry which may have impacted clinical decisions and outcomes. For the purposes of this study, we did not collect data about medication exposure surrounding pupillary measurements, aside from excluding patients with exposure to inhalational anesthetics (sevoflurane) at the time of pupillary measurements. Nonetheless, medications which may confound an accurate exam include high-dose opioids, neuromuscular blockade, and alpha-2 receptor agonists, all of which are commonly used in pediatric critical care [29]. Pertaining to the degree of functional impairment experienced by survivors, we assessed discharge FSS score but did not measure a baseline. Up to 65% of neonatal and pediatric patients placed on ECMO

have chronic underlying conditions that would affect their baseline functional status; therefore, our methods may have overestimated the true burden of injury in the survivors [30]. For this study, we also were not able to compare a baseline pre-ECMO NP_i and did not evaluate temporal trends. Therefore, we were unable to determine whether timing from cannulation affected outcome, or whether improvement in NP_i was associated with better outcomes compared to NP_i values that declined or remained persistently low. This approach may have overlooked an important interaction between dynamic pupillary changes and outcomes.

Conclusion

In our single-center study, our exploratory analysis showed that a minimum NP_i of less than 3 in the first 72 h after initiation of ECMO support is strongly associated with death. Our study suggests that automated pupillometry may be a useful tool in the multimodal approach for early neuro-prognostication of pediatric patients requiring ECMO. Large, multicenter, prospective studies are needed to validate these findings.

Abbreviations AP: Automated pupillometry; AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; ECPR: Extracorporeal cardiopulmonary resuscitation; EEG: Electroencephalography; EHR: Electronic health record; FSS: Functional Status Scale; ICU: Intensive care unit; IQR: Interquartile range; NP_i: Neurologic Pupil Index; NP_i-min: Minimum Neurologic Pupil Index; OR: Odds ratio; PICU: Pediatric intensive care unit; pSOFA: Pediatric Sequential Organ Failure Assessment; ROC: Receiver operating characteristic; VA: Venoarterial; VV: Venovenous

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Data Availability The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study was approved by the University of Texas Southwestern Institutional Review Board (STU-2019-1424; automated pupillometry in pediatric patients, approved 12/1/21) and conducted in accordance with the ethical standards of the Committee for the Protection of Human Subjects. A waiver of informed consent was granted given the non-interventional nature of this study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Molly McGetrick¹ · Nicolle Diaz² · Xilong Li³ · Tyler Terrill⁴ · Kari Powers⁵ · Rana Said⁴ · Deepa Sirsi⁴ · Lakshmi Raman² · Darryl Miles²

✉ Molly McGetrick
Molly.mcgetrick@UTSouthwestern.edu

¹ Division of Cardiology, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

² Division of Critical Care Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA

³ Peter O'Donnell Jr. School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA

⁴ Division of Neurology, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA

⁵ Children's Medical Center, Dallas, TX, USA