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The association between neurologic pupillary index (NPi) and functional outcomes in critically ill children

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Abstract

Background Automated pupillometry is a novel technology which can measure pupillary dynamics objectively at the bedside in critically ill patients. The Neurologic Pupil Index (NPi), a composite metric derived from pupillary reactivity parameters, has been proposed as a more objective measure of pupillary function and a potential prognostic tool in neurocritical illness. We hypothesized that the minimum NPi (NPi_{min}) measured in critically ill children would correlate with functional outcome at hospital discharge.

Methods This was a single-center retrospective observational cohort study of patients admitted to the pediatric intensive care unit (PICU) with primary brain injury or risk of secondary brain injury. The NPi_{min} reported during the PICU admission was compared with measures of outcome. Unfavorable outcome was defined by death or a change in functional status scale (FSS) score of ≥ 3 points from baseline to hospital discharge, whereas favorable outcome was alive and change in FSS score < 3).

Results Automated pupillometry data were extracted from one-hundred and six patients, 77 (72.6%) of whom had a primary neurologic diagnosis and 25.5% of whom died. The NPi_{min} was significantly lower in children who experienced an unfavorable outcome compared to those with a favorable outcome (0.8 vs. 3.7; $p < 0.001$). Prognostic performance of NPi_{min} for unfavorable outcome was assessed using logistic regression which demonstrated an area under the receiver operative curve (AUROC) of 0.82 and optimal NPi_{min} threshold of ≤ 2.1. When patients with an NPi_{min} of 0 were excluded, NPi_{min} best predicted unfavorable outcome at a higher NPi threshold of ≤ 3.5 with an AUROC of 0.72.

Conclusion Minimum NPi values were strongly associated with functional outcome at hospital discharge in a single-center cohort of critically ill children. Further research may reveal a role for NPi as an objective bedside biomarker that could enhance pediatric-specific prognostic models.

Keywords Pediatrics, Critical care, Pupillometry, Brain injury, Prognostication, Outcomes, Neuromonitoring

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Background

Medical advances in pediatric critical care have improved the likelihood of survival after critical illness, yet 25% of children who survive develop new functional or cognitive impairment [1, 2]. During acute illness, clinicians often use available information to guide collaborative discussions with families about prognosis, potential medical and surgical interventions and to discuss goals for life sustaining therapies. Often these discussions in acute illness surround neurological prognostication which can be particularly challenging in the early stages of illness. In addition to clinical exam findings, neurologic scoring systems and neuroimaging, the development of reliable predictive tools is needed to help guide medical decision making and expectations. Algorithms such as the Pediatric Risk of Mortality III Score (PRISM-III) and Pediatric Index of Mortality (PIM) calculate mortality risk using physiologic data collected during the first hours of PICU admission, such as laboratory values, vital signs and subjective pupillary assessments [3, 4]. However, these assessments fail to capture the impact of clinical events that occur later in the hospitalization and inconsistently correlate with functional outcomes in survivors [3, 5, 6]. Neurological injury and transient neurological dysfunction are common among critically ill children, and when present they are highly associated with new morbidity and mortality. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain are often utilized in prognostic prediction [7, 8]. These tools provide valuable and objective data about brain structure and function, but are resource intensive, require expert interpretation and may only provide information about a discrete point in time. Conversely, the pupillary light reflex (PLR) is a simple, low-cost bedside clinical exam which tests the integrity of the third cranial nerve, optic and midbrain pathways and can be repeated serially in a patient with an evolving clinical status. Importantly, early detection of abnormal pupillary reactivity can provide a therapeutic window to detect deterioration and prompt changes in clinical management.

The current gold standard assessment of the PLR relies on subjective examiner interpretation of the pupillary size, shape and response to a lighted stimulus, described as normal, sluggish or non-reactive. In contrast, the automated pupillometer (AP) measures static and dynamic components of the PLR with near perfect inter-examiner reliability and is minimally influenced by subjective interpretation, environmental conditions such as light stimulus to the contralateral eye, or patient factors such as iris color [9, 10]. The neurologic pupillary index (NPi) is a unitless measurement calculated by comparing a patient's pupillary size and reactivity to established normative and abnormal values of pupil reactivity measured in adult cohorts [11]. There is increasing evidence supporting the utility of the NPi in outcome prediction in various forms of acute brain injury in adults from intracranial hypertension, subarachnoid hemorrhage, and hypoxic-ischemic injury [12–21]. As a result, AP is now used in many intensive care units and is recognized as a potential prognostic tool after cardiac arrest by American Heart Association and the European Society of Intensive Care Medicine [22, 23]. Automated pupillometry is considered safe for use in children and is quickly becoming a standard in neurological assessments in pediatric intensive care units, but there is little data on its utility as a prognostic tool. As with adults, pupillometry may provide a non-invasive measure of both neurological function and prognosis in children, but incorporation of AP measurements into pediatric specific prognostic models would require rigorous studies of the tool within this population and within the context of different disease pathologies [24].

Our objective was to conduct a pilot study investigating the prognostic performance of the NPi in forecasting discharge outcomes in children with primary brain injury or risk of secondary brain injury admitted to the PICU who received automated pupillometry. We hypothesized that the lowest NPi measured during the intensive care unit admission would correlate with discharge outcome, such that children with lower minimum NPi (NPi_{min}) values would be more likely to experience an unfavorable outcome or suffer severe disability or death during hospital admission. These data aim to evaluate whether AP and the NPi may serve as useful adjuncts in future prospective studies that incorporate objective NPi measurements, rather than subjective pupillary assessments, into pediatric outcome prediction models.

Methods

Study design and population

This single-center retrospective observational cohort study was conducted in a 44 bed PICU at Children's Medical Center Dallas, a free-standing children's hospital affiliated with the University of Texas Southwestern Medical Center (UTSW) in Dallas, Texas, USA. In 2018 we introduced AP to the PICU and generated an institution-specific guideline recommending its use with clinical assessments for patients with a primary neurologic diagnosis or those with a non-primary neurologic diagnosis who were at risk for secondary neurologic injury including patients with (1) severe hypoxemia from acute respiratory failure, (2) cardiogenic or septic shock, (3) severe metabolic dysfunction such as liver failure and diabetic ketoacidosis, (4) marked coagulopathy with risk for intracranial hemorrhage and (5) any patient requiring extracorporeal membrane oxygenation (ECMO). Additional patients who did not meet these criteria may be examined with pupillometry at the discretion of the

clinical team. All PICU patients who received AP during neurological assessments between December 2019 and February 2021 were eligible, except for patients diagnosed with congenital or acquired abnormalities of the eye or surrounding soft tissue (Fig. 1). This study was approved by the UTSW institutional review board (IRB) (STU-2019–1424; automated pupillometry in pediatric patients, approved 12/1/21) and procedures were conducted in accordance with the UTSW IRB's outlined ethical standards on the conduction of human research and with the Helsinki Declaration of 1975 [25]. Due to the retrospective nature of the study, the UTSW institutional review provided a waiver of informed consent.

Clinical data and outcome measures

Demographic and clinical data extracted from the medical record included age at admission, sex at birth, and lengths of stay. Patients were grouped by primary admission diagnosis, classified as neurological or non-neurological. Neurological diagnoses were conditions which impacted central nervous system (CNS) functioning, including traumatic or spontaneous CNS hemorrhage, hypoxic-ischemic injury, brain tumor, acute ischemic stroke, infection of the central nervous system, inflammatory encephalopathy and metabolic encephalopathy. Non-neurological diagnoses included respiratory failure, septic shock, cardiogenic shock, hemorrhagic shock and multiorgan failure. The extent of impaired consciousness and predicted risk of mortality was documented using the admission Glasgow Coma Scale (GCS) and the PRISM-III score, respectively.

The pre-illness Functional Status Scale (FSS) score and FSS at hospital discharge were calculated for each patient retrospectively using data from the medical record. The FSS quantifies function in six domains: motor, communication, sensation, mental status, respiratory support, and feeding [26]. Each domain was scored on a 5-point scale, ranging from 1 (normal function) to 5 (very severe

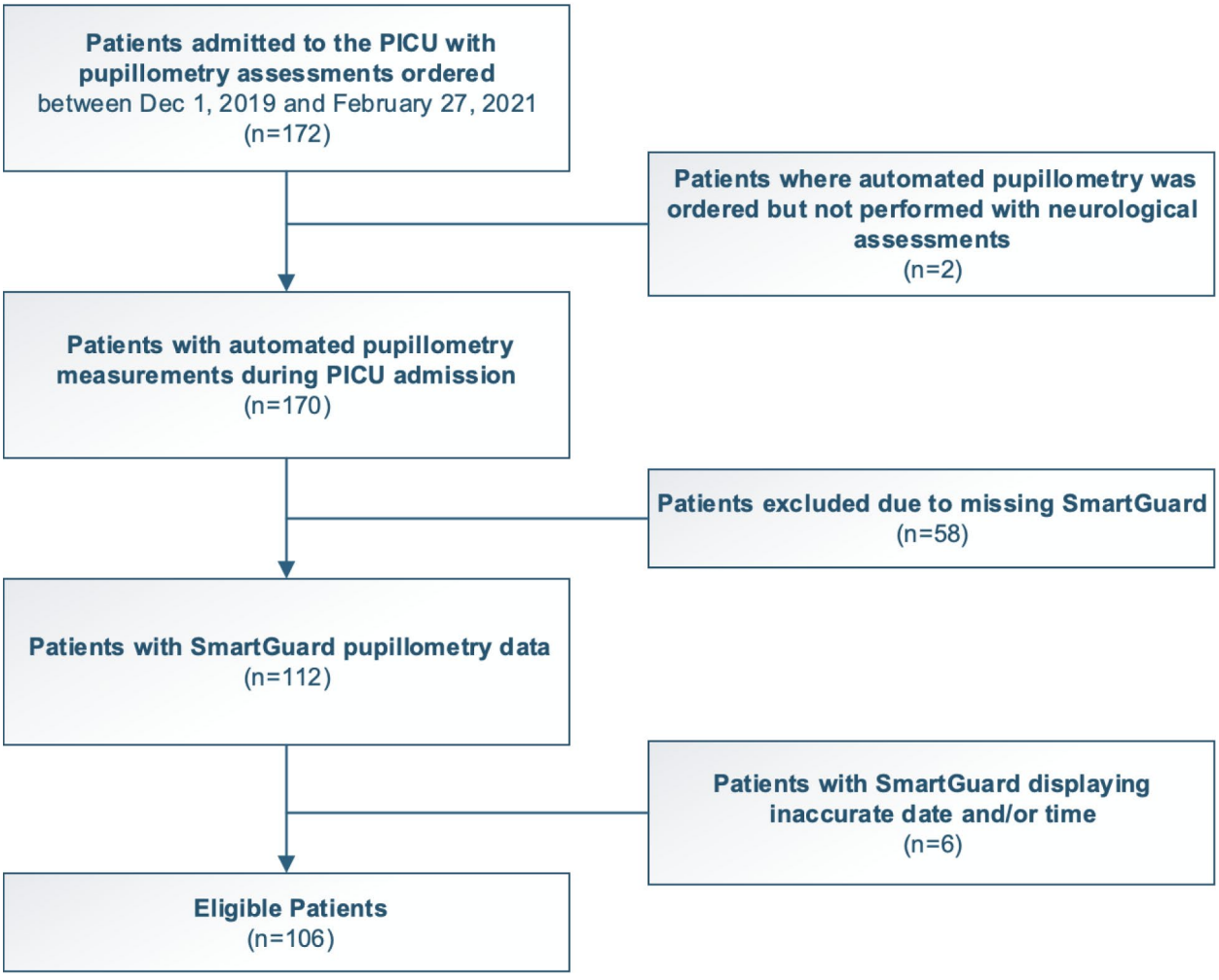


Fig. 1 Flowchart of patient enrollment in the pupillometry study. The SmartGuard is an accessory for the pupillometer that ensures pupillary scans are performed at a standardized distance from the eye and automatically records and timestamps each measurement

dysfunction). Baseline FSS score was based on pre-morbid condition, where 6–7 = normal; 8–9 = mildly abnormal; 10–15 = moderately abnormal; 16–21 = severely abnormal and > 21 = very severely abnormal [26]. Patients without prior impairments were assigned a baseline FSS of 6. A favorable outcome was defined as survival to discharge with a change in FSS score of < 3 points from baseline. Unfavorable outcome was death or FSS score ≥ 3 points higher at discharge compared to baseline, as previously described [27]. Secondary outcome groups were severe disability (SD) versus no severe disability (NSD) (total discharge FSS ≥ 16 points or death vs. FSS < 16 and alive) and dead versus alive at discharge.

Quantitative pupillary measurements

NPi was measured by a bedside nurse using the NPi-200 AP (NeurOptics®, Irvine, Ca, USA) fitted with a patient-specific SmartGuard attachment which maintained a fixed distance of the device from the eye during scanning. NPi measurements were timestamped and stored within the SmartGuard using smart card technology and were also entered into the patient's electronic medical record nursing flow sheet for clinical documentation. For data analysis, NPi data was collected from the SmartGuard attachments after patient discharge from the PICU and was uploaded to Microsoft excel spreadsheet. From pooled patient data, the NPi_{min} was defined as the lowest NPi for either the left or right eye during the measurement period. The standard prescribed frequency was every 2–6 h. While most providers began measurements at the time of PICU admission, AP could start at any time per clinician discretion. Based on the manufacturer's algorithm, NPi values range from 0 to 4.9, where 0 is a non-reactive pupil, < 3 is considered sluggish or abnormal and 3–4.9 is a normal response [11]. NPi_{min} for each patient was included in the analysis, but we excluded an NPi = 0 if the subsequent NPi was ≥ 1 point higher within 2 min, as this likely corresponded to measurement error. No complications associated with the device were reported during the study.

Data analysis

Analyses and construction of figures were performed in R (version 4.3.0), Microsoft excel, and PRISM GraphPad (version 10.4.2). Summary statistics were presented for demographic and clinical data, stratified by favorable (change in FSS score of < 3 points from baseline) vs. unfavorable outcome (change in FSS score of ≥ 3 points from baseline), severe disability vs. no severe disability (total discharge FSS ≥ 16 points or death vs. FSS < 16 and alive) and dead vs. alive. Continuous variables were presented as counts and percentages, while numerical data were presented as mean and standard deviation if the data were normally distributed and median and range otherwise. To test for differences between groups, a chi-square test was used for categorical data and for numerical data a t-test was used if the assumption of normality was verified and a Mann–Whitney U test otherwise. Significance was defined by p-values of < 0.05. NPi_{min} for each patient was applied to receiver operating curve (ROC) analysis to assess predictive accuracy for the outcomes of interest. Optimal NPi thresholds for predicting outcome were calculated using Youden's J statistics. Lastly, we sought to understand the impact of other illness variables on the NPi_{min}, incorporating total PRISM-III score, categorical neurological diagnosis, PICU length of stay (LOS), and GCS into our analysis. Because of the substantial number of NPi_{min} values of 0 in the dataset, each NPi_{min} was first scaled to lie between zero and one where the NPi_{min} was first divided by the maximum NPi of 4.9. Then, a zero-inflated beta regression model was fitted with covariates corresponding to these variables. Internal validity of the FSS was assessed by comparing calculated admission and discharge FSS scores from two physician raters from pediatric critical care and physical medicine and rehabilitation (MM and CS) for 60 patients. Cohen's kappa was calculated to assess for agreement in each of 6 domains and a margin of agreement of ± 1 point for combined FSS was deemed acceptable agreement for this test. This showed excellent inter-rater agreement for total FSS score at admission (K = 0.98) and discharge (K = 0.8). Additional outcome analysis was performed using patients with baseline FSS of 6 or 7 points and those who had NPi_{min} greater than zero.

Results

Demographic, clinical and outcome data

One hundred and six study participants were included. Descriptive statistics stratified by the outcome group are shown in Table 1. The median age for the 106 study participants was 11.3 years. Seventy-seven (72.6%) had a primary neurologic diagnosis, the most common of which was traumatic brain injury (29.2%). Twenty-nine patients had non-neurological diagnoses including respiratory failure (11), toxic ingestion (8) and septic shock (4). Eighty-nine children (84%) had normal or near normal baseline FSS scores (6–7), while 3 patients had severe baseline disability (FSS ≥ 16) (Table 2). Ultimately, forty children (37.7%) experienced a favorable outcome and 66 (62.3%) suffered an unfavorable outcome, of whom 27 died, 12 survived with a severe disability and 27 had no severe disability. As expected, PRISM-III scores were higher in patients who experienced an unfavorable vs favorable outcome (16 vs. 11; $p < 0.0001$), and children with unfavorable outcomes had longer ICU length of stay (3.5 vs. 12 days; p = 0.0001) and hospital LOS (8.5 vs. 18.5 days; p = 0.003).

Table 1 Demographic and clinical data stratified by outcome group

	Unfavorable Outcome			Severe Disability			Death		
	No	Yes	p	No	Yes	p	No	Yes	p
n	40	66		67	39		79	27	
Female, n (%)	18 (45)	33 (50)	0.77	30 (44.8)	21 (53.8)	0.48	37 (46.8)	14 (51.9)	0.82
Age, years, med (min, max)	12.6 (0,21.9)	9.9(0.2,18.5)	0.50	11.5(0.01,21.9)	9.8 (0.3,18.5)	0.60	11.3(0, 21.9)	12.5(0.3,18.5)	0.70
PICU LOS med (min, max)	3.5 (1, 19)	12 (1, 50)	0.0001	6 (1, 37)	10 (1, 50)	0.11	7 (1, 50)	5 (1, 41)	0.61
Hospital LOS med (min, max)	8.5(1, 51)	18.5(1,167)	0.003	13(1, 79)	14(1, 167)	0.97	16 (1,79)	5 (1, 167)	0.02
PRISM-III med (min, max)/mean (SD)	11(0, 28)	16(0, 48)	< 0.0001	13.1(6.7)	20.5(10.6)	0.0003	13.9 (7.1)	21.5(11.5)	0.003
Minimum NPi med (min, max)	3.7 (0, 4.9)	0.8 (0, 4.5)	< 0.0001	3.3 (0, 4.9)	0 (0, 3.7)	< 0.0001	3.2 (0, 4.9)	0 (0, 3.3)	
Neuro Diagnosis, n (%)	28 (70.0)	49 (74.2)	*0.08	48 (71.6)	29 (74.4)	*0.94	60 (75.9)	17 (63)	*0.29
Traumatic Brain Injury	13 (32.5)	18 (27.3)		19 (28.4)	12 (30.8)		27 (34.2)	4 (14.8)	
Hypoxic Ischemic Injury	1 (2.5)	11(16.7)		3 (4.5)	9 (23.1)		5 (6.3)	7 (25.9)	
Brain Tumor	2 (5)	8 (12.1)		5 (7.5)	5 (12.8)		6 (7.6)	4 (14.8)	
Spontaneous ICH	3 (7.5)	4 (6.1)		6 (9)	1 (2.6)		6 (7.6)	1 (3.7)	
Inflammatory Encephalopathy	5 (12.5)	1 (1.5)		6 (7.6)	0 (0)		6 (7.6)	0 (0)	
Metabolic Encephalopathy	3 (7.5)	3 (4.5)		5 (7.5)	1 (2.6)		5 (6.3)	1 (3.7)	
CNS infection	1(2.5)	3 (4)		3 (4.5)	1 (2.6)		4 (5.1)	0 (0)	
Acute Ischemic Stroke	0 (0)	1 (1.5)		1 (1.5)	0 (0)		1 (1.3)	0 (0)	
Non-Neuro Diagnosis, n (%)	12 (30)	17(25.8)		19 (28.4)	10 (25.6)		19 (24.1)	10 (37)	
Respiratory Failure	3 (7.5)	8 (12.1)		6 (9)	5 (12.8)		6 (7.6)	5 (18.5)	
Toxic Ingestion	7 (17.5)	1 (1.5)		8 (11.9)	0 (0)		8 (10.1)	0 (0)	
Septic Shock	0 (0)	4 (6.1)		1 (1.5)	3 (7.7)		1 (1.3)	3 (11.1)	
Cardiogenic Shock	1 (2.5)	1 (1.5)		2 (3)	0 (0)		2 (2.5)	0 (0)	
Hemorrhagic Shock	0 (0)	1 (1.5)		0 (0)	1 (2.6)		0 (0)	1 (3.7)	
Multiorgan Failure	0 (0)	1 (1.5)		0 (0)	1 (2.6)		0 (0)	1 (3.7)	
Other	1 (2.5)	1 (1.5)		2 (3)	0 (0)		2 (2.5)	0 (0)	

Unfavorable outcome: a change in functional status scale (FSS) score from admission to hospital discharge of ≥ 3 points; Favorable outcome: a change in FSS of < 3 points from admission to hospital discharge; Severe Disability: FSS of ≥ 16 points at hospital discharge; Death: died during admission; *p-values represent the significance of having a primary neurological diagnosis over non-neurological diagnosis on the outcome

Table 2 Functional status scores at admission and discharge and outcomes

Functional Status Score, n (%)	Admission	Discharge
FSS 6—7	89 (84)	27 (25.5)
FSS 8—9	9 (8.5)	17 (16)
FSS 10—15	5 (4.7)	22 (20.8)
FSS 16—21	1 (0.9)	12 (11.3)
FSS > 21	2 (1.9)	28 (26.4)
Outcomes, no/total cohort (%) for all		
Favorable outcome		40 (37.7)
Unfavorable outcome		66 (62.3)
Non-severe, alive		27 (25.5)
Severe, alive		12 (11.3)
Dead		27 (25.5)

FSS Functional Status Scale

Favorable outcome is a change is FSS from admission to discharge of < 3 points, Unfavorable outcome is a change is FSS of ≥ 3 points, and Severe outcome is a discharge FSS of > 16 points

FSS Functional Status Scale

NPi data

The analysis encompassed 5,284 paired NPi measurements, with a median of 92 assessments per patient (interquartile range: 55–156). Patients with unfavorable outcomes had a significantly lower median NPi_{min} than those with a favorable outcome (0.8 vs. 3.7; $p < 0.0001$) as displayed in Fig. 2. Similarly, we observed a significant difference in the median NPi_{min} between patients with severe disability and no severe disability (0 vs. 3.3, $p < 0.0001$), and dead versus alive at discharge (0 vs. 3.2, $p < 0.0001$). Using logistic regression, our model demonstrated that NPi_{min} predicted all outcomes of interest with good accuracy (unfavorable outcome: AUROC = 0.82 (sensitivity 79%, specificity 73%), severe disability: AUROC = 0.88 (sensitivity 72%, specificity 88%), and death: AUROC = 0.88 (sensitivity 86%, specificity 78%) (Fig. 3A). The predictive thresholds with best combined sensitivity and specificity for unfavorable outcomes, severe disability and death were ≤ 2.1, ≤ 1.6 and ≤ 0.7, respectively. When the 89 patients with baseline FSS of 6–7 indicating normal or near normal functional status were analyzed separately NPi_{min} showed stronger predictive accuracy. The predictive thresholds were: unfavorable outcome ≤ 2 (AUROC 0.85, sensitivity 74%, specificity 84%); severe disability ≤ 0.9 (AUROC 0.90, sensitivity 83%, specificity 85%); and death ≤ 1 (AUROC 0.91, sensitivity 95%, specificity 74%) (Supplement 1).

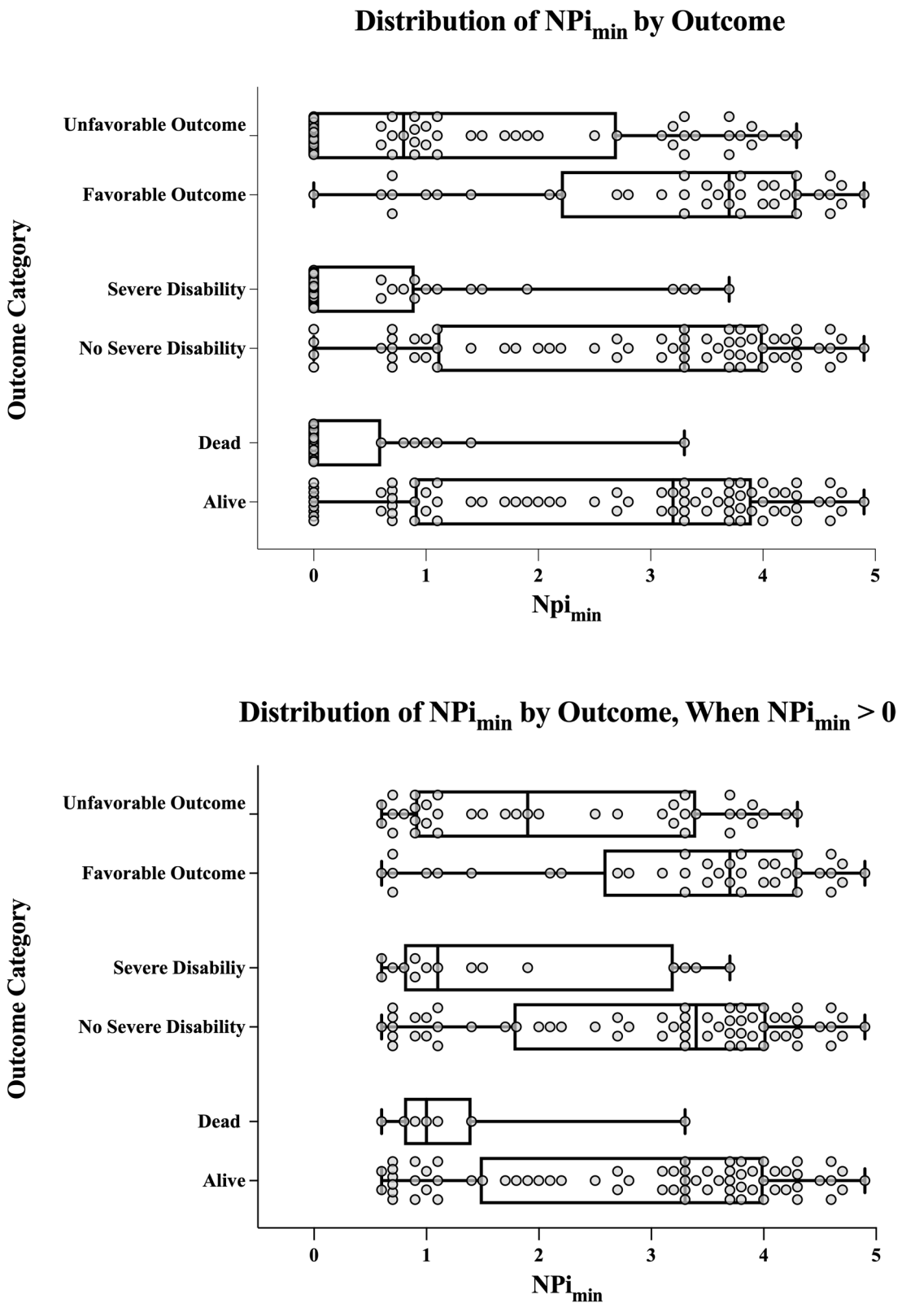


Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Distribution of minimum Neurologic Pupil Index (NPi) measurements by outcome group. Each dot represents an individual patient's NPi_{min} value. Overlying box-and-whisker plots indicate the minimum, first quartile (Q1), median (Q2), third quartile (Q3), and maximum for each outcome group. The top panel shows the distribution for all 106 patients. Median NPi_{min} values were: unfavorable outcome 0.8, favorable outcome 3.7, severe disability 0, no severe disability 3.3, dead 0, and alive 3.2. Comparisons between paired groups (unfavorable vs. favorable, severe disability vs. no severe disability, and dead vs. alive) were all statistically significant ($p < 0.001$). The bottom panel: distribution for the 77 patients with $NPi_{min} > 0$. Median NPi_{min} values were: unfavorable outcome 1.9, favorable outcome 3.7, severe disability 1.1, no severe disability 3.4, dead 1.0, and alive 3.3. Differences between the same paired groups remained statistically significant ($p < 0.001$ for all)

Twenty-nine patients (27.3%) had a $NPi_{min} = 0$, of whom 21 died, 4 survived with a severe disability, 3 survived without severe disability and only 1 had a favorable outcome. Notably, the only patient with an NPi_{min} of 0 who achieved a favorable outcome was a child diagnosed with toxic encephalopathy secondary to an accidental baclofen overdose, who subsequently demonstrated progressive normalization of NPi values with supportive care. Given the high proportion of patients with $NPi_{min} = 0$, a sensitivity analysis was performed which modeled the performance of NPi_{min} when patients with a NPi_{min} of 0 were excluded (Fig. 2). In this cohort of 77 patients, NPi_{min} remained a predictor of outcome, albeit with slightly diminished accuracy (Table 3, Fig. 3B): unfavorable outcome: AUROC = 0.72 (sensitivity 61%, specificity 76%), severe disability: AUROC = 0.77, (sensitivity 74%, specificity 73%), and death: AUROC = 0.8 (sensitivity 76% specificity 86%). Within this subgroup, the optimal cutoff points for which NPi_{min} predicted outcome were unfavorable outcome: ≤ 3.5, severe disability: < 2, death: ≤ 1.5 (Table 3).

The multivariate regression model investigated the relationship between relevant covariates and NPi_{min} (Table 4). Increasing PRISM-III score correlated with a higher likelihood of a non-reactive pupil, and the addition of each point to the total PRISM-III score increased the probability of $NPi_{min} = 0$ by 14.2%. The impacts of neurological over non-neurological diagnosis, ICU LOS and admission GCS were not significant. In patients where NPi_{min} was > 0, the only covariate which negatively correlated with observed NPi_{min} was ICU LOS (p = 0.046). Clinically this translates into a decrease in NPi_{min} of 0.5 for every 20 days in the ICU.

Discussion

This is one of the first studies exploring the role of NPi as a prognostic biomarker in critically ill children with and without neurological injury. In our exploratory study, we found a convincing association between minimum NPi (NPi_{min}) and outcome that warrants further investigation in a larger prospective study. Compared to those children with favorable outcomes, the NPi_{min} during PICU admission was significantly lower in children with unfavorable discharge outcomes defined by measurable functional status scale score change, and among those who developed severe disability or died before hospital discharge. The NPi_{min} independently predicted all outcomes of interest with reasonable accuracy, yielding AUROC values greater than 0.8 for all categories, and the strongest performance in patients with normal or near normal admission functional status scale scores.

Notably, more than one-fourth of the cohort were classified as having a non-reactive pupil ($NPi_{min} = 0$), with no indication that this was due to device malfunction or measurement error. Given the known association between absent pupillary reactivity and poor neurological outcomes, it was not surprising that 90% of these children died or suffered severe disability [20, 28, 29]. A secondary analysis excluding these patients continued to show significant differences in NPi_{min} between those with favorable versus unfavorable outcomes and between survivors and non-survivors. For all patients in the study, the optimal NPi_{min} cutoff for predicting unfavorable outcome was ≤ 2.1, but this threshold increased to ≤ 3.5 when we excluded patients with NPi_{min} of 0. In our cohort, although the median NPi_{min} differed significantly between outcome groups, there was considerable overlap in NPi_{min} values across these groups. Therefore, caution is warranted when interpreting specific threshold values for outcome prediction. One reason for this is that children with and without a primary neurological diagnosis were included. The rationale for including a diverse patient population was that children requiring ICU care for non-neurological conditions may still experience secondary neurological injuries due to various illness-related or treatment-induced factors, potentially affecting pupillary dynamics and overall outcome. As a result, factors that determine mortality or unfavorable outcomes could be due to multiorgan or system failure or other withdrawal of care decisions that are not necessarily dependent on pupillary reactivity. Larger studies examining the role of NPi_{min} in specific patient populations, such as traumatic brain injury or hypoxic-ischemic brain injury, may help in elucidating more rigorous and accurate threshold values.

Adult literature has consistently shown that NPi predicts outcomes after critical illness. The large multicenter prospective ORANGE study demonstrated that any NPi < 3 in the first week of ICU admission was associated with death or poor neurologic outcome 6 months after acute brain injury [28]. Utilizing similar methods to our study, other authors have defined NPi thresholds of ≤ 3.4 for prediction of severe disability after brain injury [30]. In the context of adult survivors of cardiac

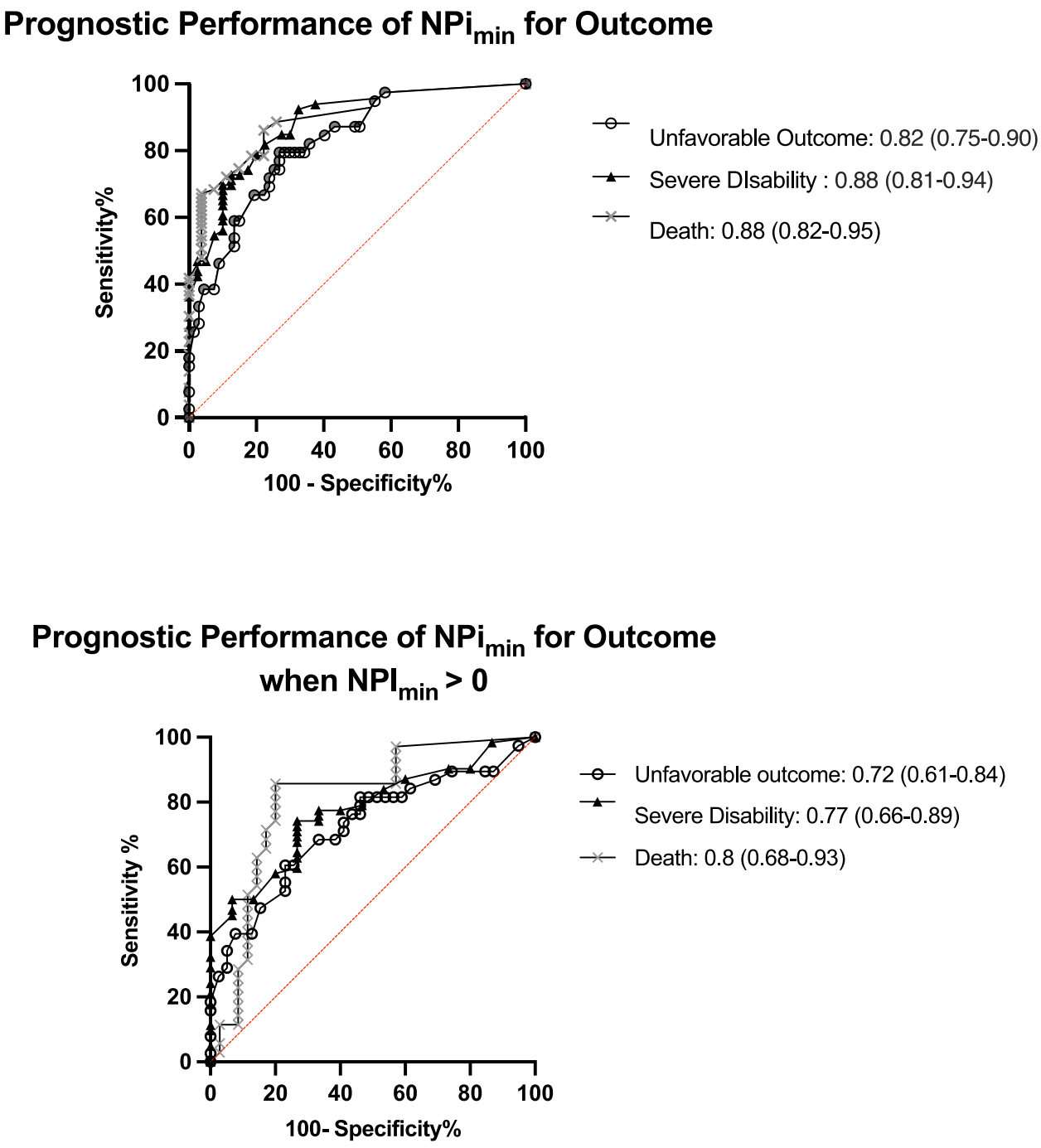


Fig. 3 Receiver operating characteristic (ROC) curve analysis of NPi_{min} for prediction of discharge outcomes. The top panel shows the ROC curves for the entire cohort of 106 patients. The lower panel shows ROC curves excluding patients with an $NPi_{min} = 0$. For each graph, curves for unfavorable outcome, severe disability, and death are plotted separately with the corresponding area under the receiver operating curve (AUROC) value and 95% confidence interval

arrest, thresholds of ≤ 3.7 within the first 6 h and ≤ 2 or ≤ 2.5 within 72 h after cardiac arrest have been associated with poor neurological prognosis [18, 20, 21]. While replication of these studies may yield similar results in pediatric cohorts, the developmental impacts of neurogenesis, orbital and optic nerve growth on pupil size and reactivity need to be more thoroughly explored. It is not yet known if and how these factors will impact the general application of NPi into pediatric prognostic models.

A small pediatric cohort study of 49 children with neurologic injuries by Jiang et. al. demonstrated that an NPi < 3 was associated with increased mortality, higher

Table 3 The logistic regression analysis for prediction of outcome using lowest NPi

Statistical Variable	All Patients ($n=106$)			Patients where NPi_{min} was > 0 ($n=77$)		
	Unfavorable Outcome	Severe Disability	Death	Unfavorable Outcome	Severe Disability	Death
AUROC (95% CI)	0.82 (0.75–0.90)	0.88 (0.81–0.94)	0.88 (0.82–0.95)	0.72 (0.61–0.84)	0.77 (0.66–0.89)	0.8 (0.68–0.93)
Optimal NPi cutoff	2.1	1.6	0.7	3.5	2.0	1.5
Sensitivity (95% CI)	79.49%(64.47–89.22%)	72.73%(60.96–82%)	86.08%(76.76-92.04%)	60.53%(44.72-74.40%)	74.19%(62.12–83.45%)	75.71%(64.50-84.25%)
Specificity (95% CI)	73.13%(61.48–82.28%)	87.5%(73.89–94.54%)	77.78%(59.24-89.39%)	76.92%(61.66-87.35%)	73.33%(48.05-89.10%)	85.71%(48.69–99.27%)
p-value	< 0.0001	< 0.0001	< 0.0001	0.0008	0.001	0.0083

Table 4 Results of the multivariate zero-inflated beta regression of NPi_{min} scaled to the [0,1] interval

	$NPi_{min}=0$		$NPi_{min}>0$	
Covariate	Estimate†	p-value	Estimate††	*p*-value
Prism III Total Score	+ 14.2%	0.0007	−0.003907	0.853
Neurological Diagnosis	−32.3%	0.521	−0.388536	0.147
ICU Length of Stay	+ 1.25%	0.572	−0.022028	0.046
GCS	−4.08%	0.543	0.030953	0.261

†Estimates presented are the percent change in the odds of a minimum NPi of zero

††Estimates presented are on the logit scale

scores on the FSS, and lower scores on the Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) scales [31]. The NPi which best predicted unfavorable neurologic outcome was ≤ 3.1 (sensitivity of 77% and specificity 81%). While our methods were similar, the populations we studied, and our definitions of unfavorable outcome differed. We enrolled children with primary neurological injury and risk of secondary brain injury and Jiang et. al. studied a more homogenous cohort with brain injury only. To further contrast, the authors defined an unfavorable outcome as a total discharge FSS score of > 12, where we used a change of 3 or more points in the FSS score from admission to discharge. Given that pupillometry utilization is growing in pediatric ICUs and poses minimal risk of harm to patients, larger prospective studies which elucidate age and disease specific NPi thresholds may be feasible.

Notably, an $NPi_{min}=0$ was highly associated with severe disability and death, yet one child from our study had an $NPi_{min}=0$ and survived with a favorable outcome. In this case, the initial NPi of 0 was most likely attributable to the profound suppressive effects of baclofen on pupillary reactivity, with subsequent recovery mirroring the course of resuscitative interventions. Thus, it is also important to consider the medication effects on pupillary reactivity when using NPi_{min} for prognostication. In the ORANGE study, authors described an NPi = 0 in 8% of their patients with favorable outcomes, and they concluded that an isolated NPi of 0 was only associated with increased mortality if it remained 0 on subsequent assessments [28]. In contrast to the ORANGE study, we excluded measurements in which the initial NPi was 0 but subsequent immediate retesting yielded significantly higher values, to minimize the influence of potential measurement error on our findings. Nevertheless, these collective findings indicate that a persistently non-reactive pupil on AP should raise concern for brain injury, but singular NPi values of 0 do not eliminate the possibility of meaningful neurological recovery.

The solid prognostic performance of NPi, even after excluding children with non-reactive pupils, highlights the potential value of incorporating quantified pupillary reactivity into predictive models and warrants further investigation. For instance, the PIM and PRISM-III scores are based upon the presence or absence of a "fixed" pupil. However, our exploratory analysis suggests that there may thresholds of abnormal reactivity which are highly associated with death or new disability. A reduced NPi suggests that while neural pathways for pupillary response remain anatomically intact, their function may be impaired by structural brain lesions, metabolic disturbances, toxins, or autonomic imbalance. For instance, a recent pediatric study proposed using pupillometry as a marker of autonomic dysregulation, finding that NPi correlated with heart rate variability—an established indicator of autonomic dysfunction and morbidity [29]. Although NPi changes in instances such as these may be transient and reversible, the clinical implications of persistent or isolated NPi changes remain unclear. Further research is needed to determine how the duration and context of NPi abnormalities may relate to long-term outcomes. Nonetheless, our findings support the potential value of NPi in enhancing the accuracy of current prognostic models.

This study has significant limitations that restrict the generalizability of its findings. This was a retrospective observational study which included a relatively small convenience sample of 106 children, most of which had high acuity of illness, defined by factors such as the need for mechanical ventilation and neuromuscular blockade. FSS score was assigned by extracting clinical information

from chart review, and this introduced possibilities for reporting errors. Although paired scoring between two examiners showed strong agreement, even minor variability in scoring may become problematic in larger cohorts. Since AP is standard of care in our PICU for patients with known or suspected neurological injury, clinicians were not blinded to NPi readings. These measurements may have influenced treatment decisions and patient outcomes. For analysis, each patient's NPimin was used to represent the point at which the pupil was least reactive. However, we did not examine trends in NPi across serial measurements. Tracking NPi changes over time, or values proximate to clinical events, could provide additional prognostic insight. Although institutional guidelines recommended AP in select patients, its timing and use were left to the discretion of the treating team. This limited our ability to assess NPi_{min} at consistent time points following PICU admission. Additionally, we included children with neurologic and non-neurological admission diagnoses, intending to capture the effects of both structural neuronal injury and autonomic nervous system dysregulation in critical illness outcomes. Although the inclusion of patients with a broad range of diagnoses was a distinctive aspect of our study, it may have limited the strength of our conclusions by incorporating cases without a primary neurologic diagnosis. However, we feel our study still highlights the potential of exploring the use of pupillometry beyond the neurocritical care population. Few publications describe the potential role for NPi in prognosis after extracranial diseases such as sepsis and COVID-19, yet pupillometry may be an interesting tool for future studies investigating autonomic balance in different forms of critical illness [32–34].

Conclusion

This single-center exploratory study of critically ill children demonstrated that lower measured NPi was associated with unfavorable hospital discharge outcomes, severe disability and death. Models which assessed predictive accuracy of the minimum NPi for unfavorable outcome performed reasonably well, even when children with non-reactive pupils were excluded. Although automated pupillometry shows promise as a prognostic tool, accurate outcome prediction at the onset of critical illness remains challenging despite established morbidity and mortality scoring systems. Larger multicenter studies are needed to establish age- and disease-specific prognostic thresholds, determine the influence of medications, and evaluate the integration of NPi into multivariable prognostic models as a reliable biomarker.

Abbreviations

NPi	Neurologic pupillary index
NPi_{min}	The minimum NPi measured during patient's admission
PICU	Pediatric intensive care unit
FSS	Functional Status Scale
AUROC	Area under the receiver operating curve
PRISM-III	Pediatric Risk of Mortality III Score
PIM	Pediatric Index of Mortality Score
EEG	Electroencephalography
MRI	Magnetic resonance imaging
PLR	Pupillary light reflex
AP	Automated pupillometry
IRB	Institutional review board
CNS	Central nervous system
GCS	Glasgow Coma Scale
SD	Severe disability
NSD	No severe disability
PCPC	Pediatric Cerebral Performance Category
POCP	Pediatric Overall Performance Category

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

M. McGetrick, D. Olson, and D. Miles contributed to the study conception and design. R Kim and C Sinn performed data collection. M. McCreary and D. Olson performed analysis and interpretation of data. M. McGetrick, A. Vashisht and R. Kim participated in drafting of the manuscript. All authors have thoroughly reviewed and approved the submission of this manuscript.

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Data availability

The dataset generated and analyzed during this current study are available in the Figshare repository, https://doi.org/10.6084/m9.figshare.29395901. Raw data is additionally available upon reasonable requests upon contact with the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the UTSW institutional review board (IRB) (STU-2019–1424; automated pupillometry in pediatric patients, approved 12/1/21) and procedures were conducted in accordance with the UTSW IRB's outlined ethical standards on the conduction of human research. Due to the retrospective nature of the study, the UTSW institutional review board provided a waiver of informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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