Quantitative Pupillometry Predicts Neurologic Deterioration in Patients with Large Middle Cerebral Artery Stroke

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Objective: This study assesses whether longitudinal quantitative pupillometry predicts neurological deterioration after large middle cerebral artery (MCA) stroke and determines how early changes are detectable.
Methods: This prospective, single-center observational cohort study included patients with large MCA stroke admitted to Boston Medical Center's intensive care unit (2019–2024). Associations between time-to-neurologic deterioration and quantitative pupillometry, including Neurological Pupil Index (NPi), were assessed using Cox proportional hazards models with time-dependent covariates adjusted for age, sex, and Alberta Stroke Program Early CT Score. Models using dilation velocity were compared with partial likelihood ratio tests. Pupillometric changes over 2-h intervals in the 12 h preceding deterioration were analyzed with linear mixed-effects modeling and Tukey's test. Matched referents (age, sex, stroke side, follow-up duration) were used for comparison. Optimal thresholds were identified using the Youden Index.
Results: Among 71 patients (mean age 66.5 years; 59.2% women), 32 (45.1%) experienced deterioration. A 1-unit decrease in NPi was associated with a higher hazard of deterioration (hazard ratio 2.46; 95% confidence interval 1.68–3.61). Dilation velocity improved model performance compared to NPi alone. NPi was significantly lower at 0–2 h (3.81 vs. 4.38, $p = 0.001$) and 2–4 h (3.71 vs. 4.38, $p < 0.001$) before deterioration compared to 10–12 h prior. Optimal thresholds were 4.01 for NPi, 0.49 mm/s for dilation velocity, and −0.15 change in NPi over 12 h.
Interpretation: Quantitative pupillometry predicts neurological deterioration in MCA stroke, with declines detectable up to 12 h prior. Dilation velocity shows promise as a novel biomarker.

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Patients with large middle cerebral artery (MCA) strokes are at risk of developing life-threatening malignant edema in up to 30% of cases.[1] Interventions such as decompressive hemicraniectomy can significantly reduce mortality in this population from 80% to as little as 20%,[2–6] but require vigilant neurologic monitoring to detect early

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signs of secondary deterioration. A key component of this monitoring is assessing pupil reactivity, as abnormalities in pupil size or response have historically been associated with catastrophic events due to increased intracranial pressure and mass effect.[7] However, it remains unclear whether quantitative pupillometry can reliably predict neurologic deterioration and how early these changes can be detected. Clarifying this relationship could enable earlier identification of neurologic decline, leading to timely interventions that may reduce morbidity and mortality.

Quantitative pupillometry, which automatically measures pupil size and reactivity, is now widely available in intensive care units across the United States.[8] The manufacturer estimates that by the end of 2024, NeurOptics quantitative pupillometers will be in over 800 US hospitals and 1,900 departments, including neuro, surgical, cardiac, and medical intensive care units, as well as emergency services. The Neurological Pupil Index (NPi) is a numeric score ranging from 0 (non-reactive) to 5 (normal), calculated using an algorithm that considers resting and constriction pupil size, percentage change in constriction size, constriction velocity, dilation velocity, and latency. This index serves as a quantitative metric of the pupillary light response. NPi has been shown to predict post-discharge outcomes for various acute brain injuries, including global anoxia, hemorrhage, trauma, and ischemia,[9,10] but often use observations that occur *after* deterioration. Our study aims to utilize quantitative, longitudinal pupillometry to determine whether changes in pupil reactivity can predict and precede neurologic deterioration in patients with MCA stroke. We hypothesize that decreased quantitative pupil reactivity serves as an early predictor of neurologic deterioration, declining several hours before clinical symptoms arise. Identifying these non-invasive signals of impending neurologic deterioration could open a window for therapeutic intervention, potentially preventing further injury and improving patient outcomes.

METHODS

Study Design and Participants

We conducted a prospective single-center observational study of adult patients with acute ischemic MCA stroke admitted to the neuroscience intensive care unit at Boston Medical Center between 2019 and 2024. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Eligible patients had stroke size ≥1/2 MCA territory evident on head CT or MRI within 72 h of admission, had at least 3 quantitative pupil observations, and presented within 24 h of stroke onset. The eligibility requirement of ≥1/2 MCA territory was determined by clinician adjudication (C.J.O., D.M.G.), with volumetric analysis[11] performed for patients with available data. Patients who had neurologic deterioration or surgery prior to their first pupil measurement were excluded. Detailed eligibility criteria are included in Figure 1.

Data Collection and Measurements

We collected demographic and clinical information including time last seen well, past medical history, procedures, and outcomes from the electronic medical record. Trained team members collected radiographic features associated with neurologic deterioration and life-threatening mass effect[12–14] including the Alberta Stroke Program Early CT Score (ASPECTS), hemorrhagic transformation, and midline shift at the septum pellucidum after establishing >80% inter-rater reliability.

Quantitative pupillometry data were collected by trained nurses using the NeurOptics NPi-200 or NPi-300 pupillometer (NeurOptics Inc., Irvine, CA) at intervals of 1, 2, or 4 h, based on the frequency of neurologic checks ordered as part of standard care initiated in the neurologic intensive care unit. The pupillometric variables measured included constriction and dilation velocity, resting and constricted pupil size, and latency. The device also calculates the NPi, which ranges from 0 to 5, with values below 3 considered abnormal by the manufacturer. We had complete data for NPi, pupil size, and constriction velocity for all patients using data from the electronic medical record. Dilation velocity and latency were available from individualized collected SmartGuards containing individual pupillometry information. Please see Supporting Information Methods for further details on data collection and ascertainment for last seen well time, imaging related variables, and pupillometric data.

Outcomes

The primary outcome was time-to-neurologic deterioration from last seen well. Neurological deterioration was

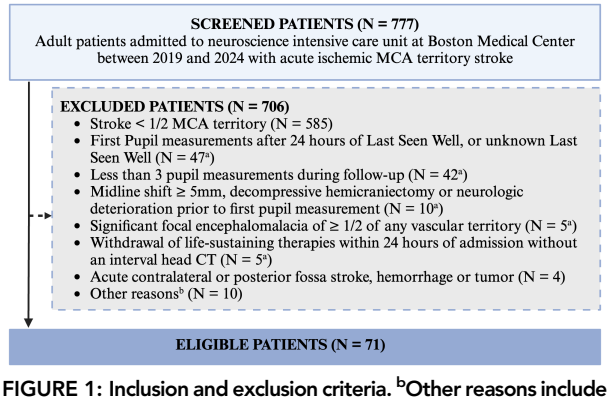

FIGURE 1: Inclusion and exclusion criteria. [b]Other reasons include history of pre-existing pupil dysfunction due to glaucoma surgery (*N* = 2), non-reactive pupil (*N* = 6), less than 6 months to live (*N* = 1), missing pupil measurement date (*N* = 1). [a] Patients may meet multiple exclusion criteria.

defined as secondary clinical decline occurring in a medical setting following initial MCA stroke injury. We used last seen well as the onset time in this patient population because of the importance of time from stroke in developing edema and subsequent deterioration. We conducted a thorough review of each patient's progress, nursing, and event notes, in conjunction with their complex assessments during their hospitalization to identify neurologic deterioration timing. All included patient medical charts were reviewed for evidence of persistent neurologic deterioration for at least 6 h or resulting in surgical decompression. Neurologic deterioration criteria consisted of Glasgow Coma Scale (GCS) score decrease ≥ 2,[15] an increase in National Institutes of Health Stroke Scale (NIHSS) score ≥ 2 (total), or ≥ 1 (motor or consciousness),[16] or a new non-pharmacologic absent pupillary reflex. Our rationale for inclusion of absent pupil reactivity as a neurologic deterioration criterion is because absent pupil reactivity is historically a subjectively identified marker of neurologic worsening and may be the only indicator in patients with severely impaired arousal. All cases were adjudicated by the principal investigator (C.J.O.). The secondary outcome included neurologic deterioration due to cerebral edema, based on review of imaging evidence of increasing midline shift and/or uncal or transtentorial herniation by 2 neurointensivists (C.J.O., D.M.G.). If death occurred in the setting of withdrawal of life-sustaining measures, it was not classified as neurologic deterioration.

Exposures and Covariates

The primary exposure was the minimum NPi of left and right eye at any time t (NPi_t). Covariates used in our multivariable model included age, sex, and ASPECTS on admission (a proxy for infarct volume).[13] We explored models with additional pupillometric characteristics, including average NPi, ipsilateral NPi, contralateral NPi, minimum dilation velocity, NPi difference, size difference, and minimum constriction velocity, all evaluated between left and right eye at each observation. Additional exploratory covariates included GCS, osmotic therapy administration, and maximum midline shift.[17–19]

Statistical Analysis

We summarized patient baseline characteristics at admission using means and standard deviations for continuous variables and frequencies and proportions for categorical variables.

Pupil observations occurring after neurological deterioration were censored, and those recorded concurrently with deterioration were also excluded from the primary Cox analysis, as the objective was to focus on prediction. For patients without neurologic deterioration who underwent withdrawal of life-sustaining therapy, we excluded observations from the 24 h preceding the last pupil measurement to avoid misclassification of undocumented neurologic deterioration. A full description of data processing is provided in the Supporting Information Methods. For patients who had volumetric imaging available, we reported the median and interquartile ranges (IQR) of their infarct volume.[11] We summarized descriptive pupil characteristics by averaging continuous variables over follow-up time and calculating the proportions of abnormal phenotypes across all observations per patient. We reported medians and IQR for within-subject pupil characteristics and compared them between groups with and without neurologic deterioration using Wilcoxon rank-sum test.

Cox Proportional Hazards Models

To assess the association between longitudinal NPi and time-to-neurologic deterioration, we used Cox proportional hazards models, treating NPi as a time-dependent covariate, adjusting for covariates listed above.[20] We first tested the proportional hazard assumption and then estimated the hazard ratio (HR) and 95% confidence interval (CI) for 1-unit changes in NPi. Post-hoc power was calculated for the primary model using Schoenfeld method.[21] Similar analyses were conducted for our secondary outcome, neurologic deterioration due to cerebral edema.

To evaluate whether including or substituting other quantitative pupil characteristics improved the models prediction of time-to-neurologic deterioration, we performed partial likelihood ratio tests[22] and reported the corresponding p-values. We also compared the non-nested Cox models using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), with lower values indicating a better balance between model fit and complexity.[23] Finally, we calculated time dependent area under the curves (AUCs) every 12 h using our final models with and without pupillometry. Further details are available in the Supporting Information Methods.

Pupillometry Prior to Neurologic Deterioration

For patients who experienced neurologic deterioration, we used violin plots to visualize the distribution of NPi observations over sequential 2- and 4-h intervals leading up to the onset of neurologic deterioration (t_0). We fit a linear mixed-effects model of NPi and designated time windows prior to neurologic deterioration that accounted for repeated measurements from individual patients.[24] We calculated and reported mean NPi values for each time interval. To compare differences in our reported means between each 2-h window and 10–12 h prior to neurologic deterioration, we used Tukey's test to adjust for multiple pairwise comparisons.[25] We applied similar methods

to analyze additional pupillometric characteristics, including dilation velocity, NPi difference, size difference, constriction velocity, and latency. To determine whether the decline in pupillometry observed before neurological deterioration was unique to patients with deterioration, we created comparable violin plots and conducted pairwise comparisons in referents matched by sex, age within 10 years, stroke side, and follow-up duration.

Optimal Thresholds of Pupillometric Change Prior to Neurologic Deterioration

We calculated the Youden Index,[26] defined as the true positive rate (sensitivity) minus the false positive rate (1-specificity), across all potential thresholds for variables such as absolute and relative changes in NPi and dilation velocity. Observations within 12 h before neurological deterioration were used for patients with deterioration, while non-overlapping 12-h intervals during the first 7 days of admission were used for patients without deterioration. The threshold maximizing the Youden Index was identified as optimal. For each variable's optimal threshold, we reported the corresponding Youden Index (where a higher value indicates better performance), along with sensitivities, specificities, and positive and negative predictive values (PPV, NPV).

We used a 2-sided significance level of $\alpha = 0.05$ for testing our primary hypothesis that decreased NPi is associated with a shorter time to neurologic deterioration. All other analyses were considered exploratory and hypothesis-generating. Statistical analyses were conducted using R version 4.4.1 (R Core Team, 2024).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Boston Medical Center and Boston University Medical Campus Institutional Review Board (H-37699) with a waiver of patient consent, as we did not deviate from standard of care.

RESULTS

Baseline Patient Characteristics

Seventy-one patients met the final inclusion criteria and were followed for a median of 6 days (IQR 3–10 days). Patients met size eligibility criteria a median 9.1 h after presentation (IQR 0.6–14.2 h) and 13.8 h after last seen well (IQR 9.0–20.3 h). The mean age of the cohort was 66.5 ± 16.4 years, with 59.2% female. The racial composition was 29.6% White, 25.4% Black, 5.6% Asian, and 39.4% other or unknown individuals, with 18.3% identifying as Hispanic or Latino. Of the 71 patients, 32 (45.1%) experienced neurologic deterioration, with a median onset time of 46.3 h (IQR 27.9–96.5 h) after last being seen well. Patients determined to have neurologic deterioration included 29 who had GCS decrease of ≥ 2 points, and 3 who had an increase in NIHSS motor or consciousness components. Decompressive hemicraniectomy was performed in 26.8% of the population, and 31% of patients died. Causes of neurologic deterioration included increasing midline shift and/or herniation due to cerebral edema ($n = 26$), acute respiratory failure ($n = 4$), and hemorrhagic conversion without mass effect ($n = 2$). Differences between patients with and without neurologic deterioration included proportion of right-sided stroke (65.6% vs 33.3%), parenchymal hemorrhage (43.8% vs 10.3%), maximum midline shift during follow-up (5.8 ± 5.3 mm vs 2.9 ± 3.3 mm), decompressive hemicraniectomy (59.4% vs 0%), and all-cause mortality (50.0% vs 15.4%) (Table 1). All 71 patients have complete NPi, pupil size and constriction velocity data, and 59 patients had additional available dilation velocity and latency data.

Aggregate Pupil Characteristics

The median number of pupil observations per patient was 88 (IQR 50–108). There was no significant difference in the frequency of pupil observations between neurologic deterioration and non-neurologic deterioration groups over the first 3 days (median 62, 78, and 69 min vs 67, 83, and 106 min over the first 24, 24–48, and 48–72 h) (Table S5, Figure S6). The average NPi over the follow-up period did not significantly differ between patients with and without neurologic deterioration (4.29 vs 4.37). However, average dilation velocity (0.38 vs 0.74 mm/s) and constriction velocity (0.89 vs 1.52 mm/s) showed notable differences between the two groups. A detailed breakdown of pupil characteristics is provided in Table 2.

Cox Proportional Hazards Models

In our primary adjusted Cox model, we found that patients with lower NPi_t had a significantly higher risk of subsequent neurologic deterioration (HR 2.46, 95% CI 1.68 to 3.61; Table S1). Based on the estimated HR, sample size ($n = 4{,}055$), and the number of observed events ($n = 32$), the post-hoc power to detect an association at a significance level of 0.05 was calculated to be 99.6%. Similar results were observed for the secondary outcome of neurologic deterioration due to cerebral edema (Table S2). Additional adjustments for GCS, osmotic therapy, and maximum midline shift also showed a significant association between NPi_t and time-to-neurologic deterioration, but these models did not significantly improve the fit compared to the primary model (Table S3). All models satisfied the proportionality assumption. When we incorporated additional pupillometry metrics that were weakly

TABLE 1. Baseline Patient Characteristics

Variable	All $N = 71$	Neurologic Deterioration $N = 32$ 45.1%	No Neurologic Deterioration $N = 39$ 54.9%
Demographics			
Age, yr	66.5 ± 16.4	62.9 ± 15.9	69.3 ± 16.4
Female	42 (59.2%)	18 (56.2%)	24 (61.5%)
Race			
White	21 (29.6%)	8 (25.0%)	13 (33.3%)
Black	18 (25.4%)	9 (28.1%)	9 (23.1%)
Asian	4 (5.6%)	0 (0%)	4 (10.3%)
Other[a]	28 (39.4%)	15 (46.9%)	13 (33.3%)
Ethnicity			
Hispanic or Latino	13 (18.3%)	7 (21.9%)	6 (15.4%)
Not Hispanic or Latino	45 (63.4%)	18 (56.2%)	27 (69.2%)
Not reported and unknown	13 (18.3%)	7 (21.9%)	6 (15.4%)
Past medical history			
Atrial fibrillation	20 (28.2%)	7 (21.9%)	13 (33.3%)
Hypertension	43 (60.6%)	17 (53.1%)	26 (66.7%)
Prior stroke	9 (12.7%)	3 (9.4%)	6 (15.4%)
Stroke assessment			
Right sided stroke	34 (47.9%)	21 (65.6%)	13 (33.3%)
NIHSS scores at presentation	20.0 ± 6.5	20.1 ± 6.0	19.9 ± 6.9
Admission ASPECTS	5.6 ± 2.9	5.2 ± 2.7	5.9 ± 3.0
Admission ASPECTS Categories			
10–8	17 (23.9%)	5 (15.6%)	12 (30.8%)
7–4	36 (50.7%)	18 (56.2%)	18 (46.2%)
3–0	18 (25.4%)	9 (28.1%)	9 (23.1%)
Hemorrhagic Transformation	41 (57.7%	27 (84.4%)	14 (35.9%)
Petechial only	26 (36.6%)	15 (46.9%)	11 (28.2%)
Parenchymal	18 (25.4%)	14 (43.8%)	4 (10.3%)
Min Glasgow Coma Scale[d]	6.4 ± 2.9	6.5 ± 3.2	6.3 ± 2.8
Max midline shift, mm[d]	4.2 ± 4.5	5.8 ± 5.3	2.9 ± 3.3
Procedure/Treatment			
Intravenous thrombolysis[b]	14 (19.7%)	4 (12.5%)	10 (25.6%)
Mechanical Thrombectomy	54 (76.1%)	24 (75.0%)	30 (76.9%)
TICI scale ≥ 2b[c]	42 (59.2%)	21 (65.6%)	21 (53.8%)
Osmotic therapy	30 (42.3%)	16 (50.0%)	14 (35.9%)
Decompressive Hemicraniectomy	19 (26.8%)	19 (59.4%)	0 (0.0%)
Withdrawal of life sustaining therapy	26 (36.6%)	15 (46.9%)	11 (28.2%)
Outcomes			
Neurologic deterioration due to cerebral edema	26 (36.6%)	26 (81.2%)	0 (0%)
Death at discharge	22 (31%)	16 (50.0%)	6 (15.4%)

ASPECTS = Alberta Stroke Program Early CT Score; NIHSS = National Institutes of Health Stroke Scale; TICI = Thrombolysis in Cerebral Infarction.

[a]Other races, includes American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Not Recorded, Not Given or Unknown.

[b]Tissue plasminogen activator (tPA) before 2023 and tenecteplase (TNK) since 2023.

[c]TICI ≥ 2b includes TICI 2b, 2c and 3, which corresponds to either slow or normal complete visualization of the vasculature.

[d]The extreme statistics were evaluated during follow-up period from presentation to censoring time.

TABLE 2. Aggregate Pupil Characteristics

Variable	Total	Neurologic Deterioration	No Neurologic Deterioration	*p*-Value
Pupil observations[b]				
Patients, *N*	71	32	39	-
Pupil observations[d], *N*	4,059	1,509	2,550	-
Observations per patient	88 [50–108]	72 [44–106]	90 [58–109]	-
Patients with NPi = 0[a], *N* (%)	4 (5.6%)	4 (12.5%)	0 (0.0%)	-
Mean continuous measurements				
NPi	4.36 [4.07–4.61]	4.29 [3.99–4.60]	4.37 [4.15–4.62]	0.31
Dilation velocity (mm/s)[b]	0.61 [0.36–0.80]	0.38 [0.23–0.69]	0.74 [0.52–0.85]	< 0.01
NPi difference	0.21 [0.14–0.32]	0.24 [0.15–0.40]	0.20 [0.14–0.30]	0.37
Size difference (mm)	0.39 [0.29–0.52]	0.44 [0.28–0.53]	0.37 [0.30–0.50]	0.98
Constriction velocity (mm/s)[b]	1.31 [0.84–1.84]	0.89 [0.59–1.60]	1.52 [1.14–1.97]	< 0.01
Latency (s)[c]	0.26 [0.24–0.29]	0.28 [0.24–0.35]	0.26 [0.23–0.28]	0.36
Proportion of abnormal measurements				
0 < NPi < 3	0 [0–3.1]	0 [0–10.9]	0 [0–1.8]	0.27
NPi difference ≥0.7	4.1 [0–10.1]	5.5 [0–13.2]	2.9 [0–8.8]	0.46
Size difference ≥1 mm	5.6 [0–12.6]	8.5 [0–13.2]	4.3 [0–9.7]	0.28

Data are represented in median and interquartile range, unless otherwise indicated. Measurements were censored after neurologic deterioration.
[a]The observation rate of NPi = 0 in the 4 patients are 17.1%, 12.5%, 1.1%, and 0.9%.
[b]Of the 71 patients, 59 have additional dilation velocity and latency data available.
[c]Infinity values in latency variable were imputed to 3 s.
[d]Four observations that occurred at the time of neurologic deterioration were included in the aggregate analysis but excluded from the primary Cox model.

correlated with NPi (Figure S1), the best-performing models for predicting time-to-neurologic deterioration included NPi and dilation velocity (AIC/BIC 354/360) and NPi difference and dilation velocity (AIC/BIC 357/363). These models had slightly lower AIC/BIC values compared to the NPi-only model (AIC/BIC 364/369) ($p = 0.04$, $p = 0.05$). Comprehensive results are reported in Tables 3, and S4. Cox models of alternative NPi variables including average NPi, ipsilateral NPi, and contralateral NPi are included in Table S6. Further sensitivity analysis with time-to neurologic using presentation as time 0 shows similar results (Table S7). Kaplan–Meier curve and risk table over first 7 days of last seen well is included in Figure S7. Overall average AUC across 12-h intervals in 96 h of last seen well was 68.9% v. 50.9% in our final models with and without pupillometry (Figure S8).

Pupillometry Prior to Neurologic Deterioration

Violin plots in Figure 2 illustrate the decline in mean NPi over the 12 h preceding neurologic deterioration. Compared to the 10–12 h window before deterioration, mean NPi was significantly lower in both the 0–2 h (3.81 vs 4.38, $p = 0.001$) and 2- to 4-h windows (3.71 vs 4.38, $p < 0.001$). We observed similar significant declines in dilation velocity and increases in NPi difference and size difference (Figures S2 and S3). To further support that changes can be detected at clinically meaningful intervals, we alternatively present 4-h increments which continue to show a significant difference compared to the 8- to 12-h interval (Figures S4 and S5). Illustrative plots of further alternative NPi variables including average NPi, ipsilateral and contralateral NPi are included in Figure S9. NPi change in extended time window of 24 h prior to neurologic deterioration shows no significant difference between 10 and 12 h prior to neurologic deterioration and any 2-h time period prior (Figure S10).

Case-Referent Results

We matched 24 neurologic deterioration positive patients to 19 referents by age, sex, stroke side, and follow-up

TABLE 3. Comparison of Non-nested Cox Models for Neurologic Deterioration

Non-nested Cox Models[a]			
Pupillometry Exposures	**AIC**	**BIC**	***p*-Value[c]**
Primary model			
NPi only	364	369	-
Alternative models with smaller AIC or/and BIC[b]			
NPi and dilation velocity	354	360	0.04
Dilation velocity and NPi difference	357	363	0.05
NPi and constriction velocity	358	364	0.07
NPi difference and constriction velocity	361	368	0.18
Dilation velocity only	363	368	0.43
Dilation velocity and size difference	364	371	0.40

[a]All models were adjusted for age, sex, and ASPECTS.
[b]Because 59 of 71 patients have dilation velocity data available, all model comparisons were performed in the same reduced dataset ($N = 59$ patients, $n = 3{,}308$ observations).
[c]The *p*-values from partial likelihood ratio test evaluated whether non-nested Cox model with alternative pupil predictor has superior fit than the primary NPi model at one-sided significance level of 0.05.

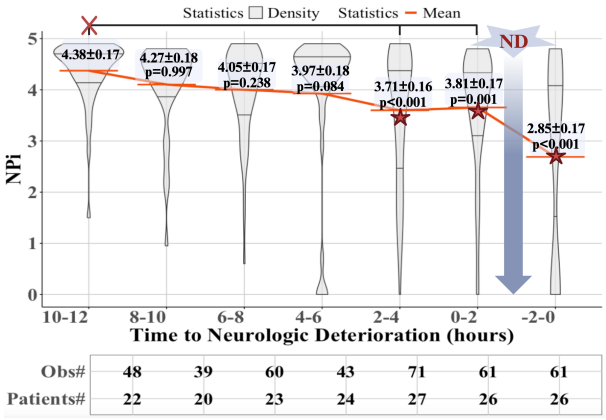

FIGURE 2: NPi declines within 12 h of neurologic deterioration. NPi was significantly lower 2–4 and 0–2 h prior to neurologic deterioration compared to 10–12 h prior. Mean NPi, standard error, and *p*-values were calculated using linear mixed-effects models. Tukey's test was used to compare mean NPi between 10–12 h and each 2-h time window up until 2 h after neurologic deterioration. *Observations occurring within 2 h *after* the event were included in −2-0 h group for visualization purpose. ND = neurologic deterioration; NPi = neurological pupil index. Created with BioRender.com.

duration from our original sample set. Each case of neurologic deterioration ($N = 32$) was matched with a non-neurologic deterioration referent ($N = 39$) based on sex (32 cases matched), age difference within 10 years (32 cases matched), and follow-up duration (31 cases matched). Further filtering for referents with the same stroke side resulted in 24 cases matches (7 cases lacked a corresponding referent). Among these 24 matches, 5 had overlapping referents, resulting in a final ratio of 24 cases to 19 referents.

In this subgroup, NPi declined significantly in both the 4–6 h (3.79 vs 4.38, $p = 0.009$) and 0–2 h (3.88 vs 4.38, $p = 0.029$) prior to neurologic deterioration compared to the 10- to 12-h time window in 24 patients with neurologic deterioration. NPi did not change significantly in the 19 time-matched referents (Figure 3). Additional illustrative 12-h time windows are included in Figure S11.

Optimal Thresholds of Pupillometric Change Prior to Neurologic Deterioration

We observed that the average NPi was 3.88 in patients 2 h prior to neurological deterioration, compared to 4.29 in non-overlapping time windows from patients without neurological deterioration. The average 12-h change in NPi was −0.63 in patients with neurological deterioration versus −0.02 in patients without. Average dilation velocity was 0.4 in the 2 h prior to deterioration, compared to 0.73 in non-deterioration patients.

A threshold of −0.15 for absolute change in NPi yielded a Youden Index of 0.40, the highest of any NPi variable (sensitivity 73%, specificity 68%, PPV 20%, NPV 96%). A threshold of 4.01 for average NPi measured 0–2 h before neurological deterioration resulted in a Youden Index of 0.25 (sensitivity 52%, specificity 73%). For average dilation velocity, a threshold of 0.49 in the 0–2 h

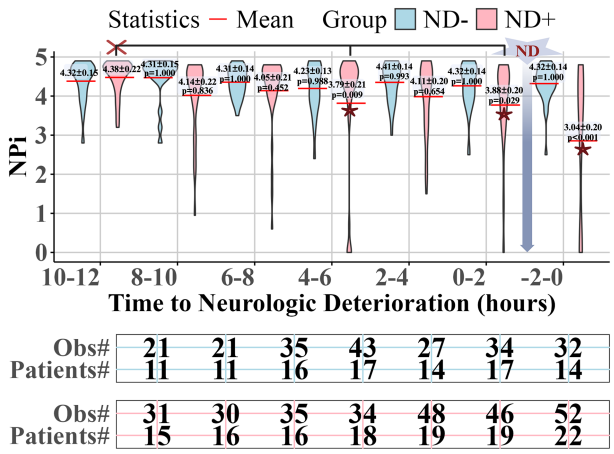

FIGURE 3: NPi across sequential 2-h time window prior to neurologic deterioration in 24 cases ($n = 1,021$) and 19 time-matched referents ($n = 837$). NPi declined significantly in both the 4–6 and 0–2 h leading up to neurologic deterioration compared to the 10–12 h time window in 24 patients with neurologic deterioration, whereas NPi didn't change significantly in patients who were 19 referents without neurologic deterioration and were time-matched with the 24 cases. The mean, standard error, and *p*-values were calculated using linear mixed-effects models. Tukey's test was used to compare mean NPi between 10–12 h and each 2-h time window following it up until 2 h after neurologic deterioration. *Observations occurring within 2 h after neurologic deterioration are included for visualization purposes. ND = neurologic deterioration; NPi = neurological pupil index. Created with BioRender.com.

before neurological deterioration achieved a Youden Index of 0.58 (sensitivity 80%, specificity 78%, PPV 28%, NPV 97%). In contrast, a change in dilation velocity of −0.02 had a lower Youden Index of 0.26, with sensitivity and specificity of 68% and 57%, respectively. Comprehensive results are included in Tables 4 and S8.

DISCUSSION

Our study demonstrates that in patients with large MCA stroke, quantitative pupillometry can predict neurologic deterioration before it becomes clinically apparent. This finding contrasts with the standard clinical practice, where pupillary changes are typically recognized only after deterioration has occurred. The lack of well-established quantitative pupillometric thresholds can create confusion, leading to unnecessary diagnostic tests for patients with an NPi below 3 and offering false reassurance for those with an NPi above 3. The decline in pupillometry starts 12 h before deterioration, with significant changes 4 h prior, offering a critical window for early intervention before clinical recognition. Our results expand on a smaller study of 30 patients, which found a significant NPi decrease at the time of neurologic deterioration compared to those without worsening,[27] and a study demonstrating that abnormal NPi can predict neuroworsening in patients with traumatic brain injury.[28] To our knowledge, this is the first study to demonstrate that quantitative pupillometry not only predicts but also precedes clinically recognized deterioration in supratentorial ischemic stroke. Notably, while we observed a decline in quantitative pupillometry over a 12-h period, the changes became significantly pronounced 4 h before neurological deterioration. We submit that a 4-h lead time represents a meaningful improvement over current standards, offering the potential for earlier and more effective interventions to reduce secondary brain injury.

Between groups, we observed a higher incidence of right hemispheric stroke in patients with neurological deterioration compared to those without (65.6% vs. 33.3%). Studies suggest that there may be an increase in impaired cardiovascular regulation due to right-sided stroke,[29,30] which may contribute to overall increased edema, injury, and potentially hemorrhagic transformation formation.[12] This finding is intriguing and should be validated in a larger study.

Notably, most aggregate pupillometry characteristics did not differ between those with and without neurologic deterioration, highlighting the importance of analyzing temporal changes to identify clinically relevant patterns. Monitoring deviations from an individual's baseline NPi may be more effective for early prediction of neurological deterioration than strictly adhering to the "abnormal" NPi <3 threshold provided by the manufacturer. The optimal absolute NPi threshold for predicting deterioration within 2 h was 4.01, with sensitivity and specificity of 52% and 73%, respectively. Sensitivity increased to 73% when the change in NPi between 10–12 and 0–2 h was −0.15. PPV for any single pupillometric threshold remained low, likely due to the low prevalence of positive cases during 12-h windows over the course of an admission. However, NPV was high across all metrics, indicating that patients with NPi >4, minimal NPi change over 12 h, and dilation velocity >0.49 mm/s are at low risk of impending deterioration. Conversely, the finding that the average NPi change within 12 h preceding deterioration was −0.63, combined with an optimal threshold for predicting neurologic deterioration of 4.01 (instead of 3), suggests that a decrease of −0.63 to values below 4 may warrant further evaluation, particularly in patients with poor arousal or other confounding factors affecting their exams.

We observed that models incorporating alternative pupil characteristics performed similarly to those using NPi, as indicated by comparable AIC/BIC values. This finding reinforces the value of NPi, given its familiarity and widespread clinical use. However, adding dilation

TABLE 4. Optimal Pupillometric Thresholds to Detect Neurologic Deterioration

Pupillometric Variables	Average Values		Optimal Threshold	Sensitivity	Specificity	Youden Index	False Positives	False Negatives	Positive Predictive Value	Negative Predictive Value
	ND	Non-ND								
NPi										
Average NPi 0–2 h before ND	3.88	4.29	4.01	52%	73%	0.25	51	12	20%	92%
Δ NPi between 10–12 and 0–2 h windows	−0.63	−0.02	−0.15	73%	68%	0.40	65	6	20%	96%
% Δ NPi between 10–12 and 0–2 h windows	−15%	1%	−3%	73%	67%	0.39	69	6	19%	96%
DV										
Average DV 0–2 h before ND	0.4	0.73	0.49	80%	78%	0.58	42	4	28%	97%
Δ DV between 10–12 and 0–2 h windows	−0.09	−0.004	−0.02	68%	57%	0.26	82	6	14%	95%
% Δ DV between 10–12 and 0–2 h windows	−9%	7%	−25%	47%	80%	0.27	39	10	19%	94%

We calculated the optimal threshold to detect ND by maximizing the Youden Index in a dataset comprised of observations from ND patients during the 12 h before ND and observations from non-ND patients from non-overlapping 12-h intervals up until 7 days of admission. For average NPi 0–2 h prior to ND there were 25 and 229 available observations in ND and non-ND patients respectively. For absolute and % Δ NPi, there were 22 and 230 available observations in ND and non-ND patients respectively. For average DV 0–2 h prior to ND, there were 20 and 196 available observations in ND and non-ND patients respectively. For absolute and % Δ DV, there were 19 and 194 available observations in ND and non-ND patients, respectively.

Δ = change; DV = dilation velocity; ND = neurologic deterioration; NPi = neurological pupil index.

velocity to the models provided a modest improvement, suggesting it may enhance predictive accuracy when combined with NPi. Notably, dynamic AUCs for predicting neurological deterioration were significantly better with pupillometry than without. These results, while promising, should be interpreted cautiously due to the limited sample size.

The increased sensitivity of dilation velocity to neurologic deterioration has not been previously reported, although it has been associated with greater disease severity.[31] We observed that average dilation velocity over time was lower in patients who experienced neurologic deterioration compared to those who did not, possibly reflecting an overall lower dilation velocity in severely injured patients. Additionally, we noted a significant decline in dilation velocity prior to neurologic deterioration (Figures S2 and S4B), a trend not observed in constriction velocity (Figures S3C and S5C). Finally, dilation velocity <0.49 mm/s had the highest Youden Index with 80% sensitivity and 78% specificity. The pathway for pupil dilation is distinct from that of pupil constriction, uniquely involving the hypothalamus, locus coeruleus, and a connection to the iris dilator muscle via the intermediolateral column of the spinal cord and superior cervical ganglion.[32] It is possible that the involvement of the hypothalamus and locus coeruleus may be more sensitive to mass effect and/or localized hydrocephalus than pupil constriction pathways involving the more well-known circuit between the optic nerve, pretectal and Edinger-Westphal nuclei, and efferent oculomotor nerve.

Known predictors of neurologic deterioration after MCA stroke are largely limited to baseline characteristics, such as infarct volume and significant carotid stenosis,[33] which are not practical for real-time patient monitoring. Although changes in longitudinal vital signs, including elevated blood pressure and decreased heart rate (as seen in Cushing's triad), can precede clinical deterioration due to increased intracranial pressure and herniation,[34] they are not currently used to predict worsening conditions. Current gold-standard monitoring relies on detecting late-stage catastrophic events through pupillary assessment, new motor

impairment, or noticeable declines in arousal. However, these indicators do not predict future, potentially preventable events. Our study suggests that pupillometry could be used proactively to facilitate early, potentially preventative interventions. This approach leverages readily available data from hundreds of intensive care units nationwide,[8] offering a valuable potential opportunity to improve patient care.

We acknowledge several limitations in our study. The single-center prospective observational cohort design may limit the generalizability of our findings to broader populations or other clinical settings. The exclusion of patients with significant encephalomalacia and pre-existing pupil dysfunction may reduce generalizability to certain patient groups. We acknowledge that because quantitative pupillometry collection began in the neurologic intensive care unit, it cannot currently detect deterioration before patients present for medical care. Additionally, our analysis relied on 12 h of available pupillometry data preceding deterioration. Data collection from electronic medical records could introduce information bias or result in incomplete data, potentially affecting the accuracy and reliability of our analyses. Only 59 out of 71 patients had complete dilation velocity and latency data. Missing dilation velocity data may introduce bias into the Cox model, especially if the data are not missing at random, potentially compromising the precision of hazard ratio estimates and diminishing statistical power. While we recoded latency to 3 s for infinity value to visualize its trend before neurologic deterioration, we are unable to quantify its association with time to the event. Future studies should prioritize complete data collection to enhance the accuracy and generalizability. Although we adjusted for confounding factors through statistical methods, residual confounding may still be present due to unmeasured or unknown variables.

Additionally, reduced pupil reactivity is not exclusively specific to evolving neurologic injury, as reactivity is influenced by other physiological factors such as pain and medications—including opioids,[35] α2-adrenergic agents,[36] and anticholinergic medications.[37] Heterogenous pupillometry frequency may have introduced measurement variability and affected the precision of our estimates. Moreover, neurologic findings may be less thoroughly documented in patients nearing withdrawal of life-sustaining therapy, potentially leading to misclassification. To mitigate, we censored pupil observations 24 h prior to withdrawal. The small sample size limited our ability to adjust for multiple confounders without risking overfitting and reduced our statistical power to perform subgroup analyses. In our temporal analysis of NPi, we were only able to compare aggregate 2-h windows in cases, not referents. To address, we conducted a small time- and subject-matched case-referent study, demonstrating a significant decline in cases and no significant change in referents. To mitigate the risk of multiple testing errors, we focused on one primary hypothesis. All others are hypothesis-generating. Finally, while patients were screened and identified prospectively, information regarding neurologic deterioration was identified retrospectively. Therefore, our results' utility as a prospective monitoring tool necessitates future study.

Despite its limitations, our study has several notable strengths. To our knowledge, this is the first study to comprehensively characterize and assess the association between longitudinal pupillometry and protocol-driven assessments of neurologic deterioration in ischemic stroke patients. The use of quantitative pupillometry data, collected through standardized protocols and equipment, enhances the reliability and objectivity of our measurements. By incorporating measurable hypothesized confounding factors, we aimed to minimize bias and improve the robustness of our findings. Additionally, our use of complementary statistical methodologies, including linear mixed-effects models and Cox proportional hazard models with time-dependent covariates, allowed for a nuanced exploration of the relationships between pupil characteristics and neurologic outcomes.

In conclusion, our findings indicate that longitudinal quantitative pupil characteristics including NPi can predict neurologic deterioration in patients with large ischemic stroke. We observed that NPi begins to decline up to 12 h prior to clinical deterioration, and that dilation velocity may be an additional unrecognized biomarker of impending deterioration. Our findings suggest that pupillometry may offer a valuable window of opportunity to predict clinical events. Understanding the patterns and trajectories of quantitative pupillometry in critically ill neurologic patients could enhance the effective interpretation of early warning signs, potentially leading to improved outcomes through timely interventions.

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Author Contributions

C.J.O. and Y.D. contributed to the conception and design of the study; C.J.O., Y.D., J.E.P., S.C., B.B., L.A.M. and R.A.S. contributed to the acquisition and analysis of data; C.J.O., Y.D., L.A.M., S.C., E.J.B., E.J.G., A.M.C-A., J.D., D.M.G., S.M.S. and S.M. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Anonymized data analyzed in this study are available from the corresponding author upon request with data use agreements.

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