JoS JOURNAL OF STROKE

Journal of Stroke 2024;26(2):321-324
https://doi.org/10.5853/jos.2023.04406

Letter to the Editor

Pupillometer-Based Neurological Pupil Index Differential: A Potential Predictor of Post-Stroke Delirium

Kotaro Noda,[1,2] Tomotaka Tanaka,[1] Soichiro Abe,[1] Ryo Usui,[1] Misa Matsumoto,[3] Yoshito Arakaki,[1] Hiroyuki Kida,[1] Ryoma Inui,[1] Kaoru Kohama,[3] Kazuo Washida,[1] Sonu M. M. Bhaskar,[1] Masatoshi Koga,[4] Kazunori Toyoda,[4] Masafumi Ihara[1]

[1]Department of Neurology, National Cerebral and Cardiovascular Center, Suita, Japan
[2]Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
[3]Department of Nursing, National Cerebral and Cardiovascular Center, Suita, Japan
[4]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

Dear Sir:

Delirium is a common complication of stroke.[1] The Intensive Care Delirium Screening Checklist (ICDSC) is used to screen patients with stroke;[2] however, relying solely on the ICDSC can be challenging when patients experience communication difficulties owing to stroke-related disorientation, aphasia, and dysarthria.[3] Furthermore, despite the strong association between cognitive function and delirium occurrence, detailed neurological examinations require professional skills, which may be difficult to perform.[2] Therefore, a simple and rapid method that is independent of cognitive function to predict delirium is needed.

NeurOptics® NPi®-200 (Neuroptics Inc., Irvine, CA, USA) is an automated pupillometer that can be used to assess and measure various pupillary light reflex parameters.[4] Using a proprietary mathematical algorithm, the NPi®-200 pupillometer calculates the neurological pupil index (NPI), which is a quantitative measure indicating the pupillary response to light stimulation.[5] Specifically, an NPI <3 and an NPI differential >0.7 between the left and right pupils have been found to be independent predictors of unfavorable outcomes in neurologically injured patients, including those with stroke.[6] However, studies on pupillometry usage to predict post-stroke delirium are limited. Herein, we aimed to fill this research gap and develop a simple and rapid method for predicting delirium in such patients.

In this retrospective, single-center, observational study, the inclusion criteria were: successful pupil evaluation on admission using an NPi®-200 pupillometer, diagnosis of ischemic stroke or intracerebral hemorrhage, and admission to the special care unit (SCU) of the National Cerebral and Cardiovascular Center, Suita, Japan. This study was approved by the ethics committee of the National Cerebral and Cardiovascular Center (study name: The Utility of Pupillometry in Acute Stroke Management, approved date: 28th December 2022, approval number: R22041). All procedures were followed in accordance with the institutional review board's ethical standards and with the Helsinki Declaration of 1975. The detailed information is described in the Supplementary Methods.

Table 1 summarizes the demographic and clinical characteristics of the study population stratified by the absence or presence of delirium. After participant selection, 131 patients with successful pupil evaluations were eligible for our analysis (Supplementary Figure 1). The mean age was 73.4±12.0 years, and 80 patients (61.1%) were male (Table 1). The prevalence of dementia was higher in the delirium group (16.0%) than in the non-delirium group (3.8%). Twenty-five patients (19.1%) developed delirium after stroke during their SCU stay. Patients with delirium had significantly higher National Institutes of Health Stroke Scale (NIHSS) scores (2 [1–5] vs. 19 [9–25], P<0.01) and lower Glasgow Coma Scale (GCS) scores (15 [15–15] vs. 12 [10–14], P<0.01) than patients without delirium. This implies that patients with more severe stroke symptoms, as measured using the NIHSS,

and those with lower GCS scores are at a significantly higher risk of developing delirium.

This study compared various pupil sizes and NPI parameters in patients with versus without delirium (Table 2). There was a trend toward a higher prevalence of patients with minimum NPI <3 in the delirium group than in the non-delirium group (5/106 [4.7%] vs. 4/25 [16.0%], *P*=0.07). The NPI differential was significantly higher in patients with delirium than in those without delirium (0.21±0.45 vs. 0.72±1.06, *P*<0.01), with a higher frequency of patients having an NPI differential >0.7 in the delirium group than in the non-delirium group (6/106 [5.7%] vs. 7/25 [28.0%], *P*<0.01). Moreover, we identified 28 patients with ischemic stroke or hemorrhage in the brainstem and cerebellum. We did not find significant association between brainstem and cerebellar damage and the abnormal NPI findings (minimum NPI <3, 5/103 [4.9%] vs. 4/28 [14.3%], *P*=0.08; NPI differential >0.7, 9/103 [8.7%] vs. 4/28 [14.3%], *P*=0.38; delirium, 21/103 [20.4%] vs. 4/28 [14.3%], *P*=0.47). In a multivariable logistic regression analysis, an NPI differential >0.7 emerged as an independent predictor of delirium (adjusted odds ratio 6.2, 95% confidence interval 1.46–26.35, *P*=0.01), while a minimum NPI <3 and pupil size did not provide significant predictive values (Figure 1). Among other parameters, the differential of maximum constriction velocity, latency of constriction, and pupil size at peak were significantly different between the groups. However, multivariable logistic regression analysis revealed no significant association between these parameters and delirium (Supplementary Tables 1 and 2).

Our findings indicate the effectiveness of the NPi®-200 pupillometer for predicting delirium in patients with stroke. Notably, the prediction model based on NPi®-200 pupillometry is independent of the presence of dementia, which is a major risk factor for delirium. Additionally, our evaluation using the NPi®-200 pupillometer was performed at the emergency department, ensuring that our results were not influenced by subsequent treatments or adverse events that could potentially lead to delirium during hospitalization. This quantitative model has considerable potential for post-stroke delirium prediction.

The role of the ascending reticular activating system (ARAS), a neural network connecting brainstem source nuclei to various brain regions, has been implicated in the development of delirium.[7] Additionally, the autonomic nervous system (ANS) influences neurotransmitters that are crucial for ARAS function.[8,9] In patients with stroke, disruptions in ARAS connectivity, coupled with ANS disturbances, can contribute to the development of delirium. Furthermore, abnormal connectivity in the arousal and attention networks of the unaffected hemisphere has been as-

Table 1. Summary of patient demographics and baseline characteristics

Characteristic	Patients without delirium (n=106)	Patients with delirium (n=25)	*P*
Age (yr)	72.8±12.0	76.1±11.8	0.22
Male sex	64 (60.4)	16 (64.0)	0.82
Medical history			
Hypertension	82 (77.4)	23 (92.0)	0.16
Dyslipidemia	63 (59.4)	18 (72.0)	0.36
Diabetes mellitus	22 (20.8)	10 (40.0)	0.07
Chronic heart disease	26 (24.5)	11 (44.0)	0.08
Chronic kidney disease	4 (3.8)	1 (4.0)	>0.99
Dementia	4 (3.8)	4 (16.0)	0.04
Stroke subtypes			0.27
Ischemic stroke	87 (82.1)	18 (72.0)	
Cardiac embolism	13	9	
Atherothrombotic infarction	17	4	
Lacunar infarction	18	1	
Others	39	4	
Intracerebral hemorrhage	19 (17.9)	7 (28.0)	
Hypertensive vasculopathy	11	6	
Cerebral amyloid angiopathy	1	0	
Other causes	7	1	
GCS	15 [15–15]	12 [10–14]	<0.01
Admission NIHSS	2 [1–5]	19 [9–25]	<0.01
Heart rate (bpm)	81.8±16.3	84.1±13.9	0.51
Systolic blood pressure (mm Hg)	162.2±31.5	162.3±29.0	0.99
Diastolic blood pressure (mm Hg)	91.1±21.2	89.0±18.5	0.67

Values are presented as mean±standard deviation, n (%), or median [interquartile range].
GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Comparison of NPI between patients with and without delirium

	Patients without delirium (n=106)	Patients with delirium (n=25)	*P*
Maximum NPI	4.43±0.59	4.52±0.24	0.47
Minimum NPI	4.22±0.78	3.80±1.17	0.03
Average NPI	4.32±0.65	4.16±0.66	0.26
Minimum NPI <3	5 (4.7)	4 (16.0)	0.07
NPI differential	0.21±0.45	0.72±1.06	<0.01
NPI differential >0.7	6 (5.7)	7 (28.0)	<0.01
Maximum pupil size (mm)	3.24±0.76	3.26±0.70	0.90
Minimum pupil size (mm)	2.92±0.64	2.74±0.56	0.20
Average pupil size (mm)	3.08±0.67	3.00±0.60	0.59
Pupil size differential (mm)	0.32±0.42	0.52±0.43	0.03

Values are presented as mean±standard deviation or n (%).
NPI, neurological pupil index.

https://doi.org/10.5853/jos.2023.04406

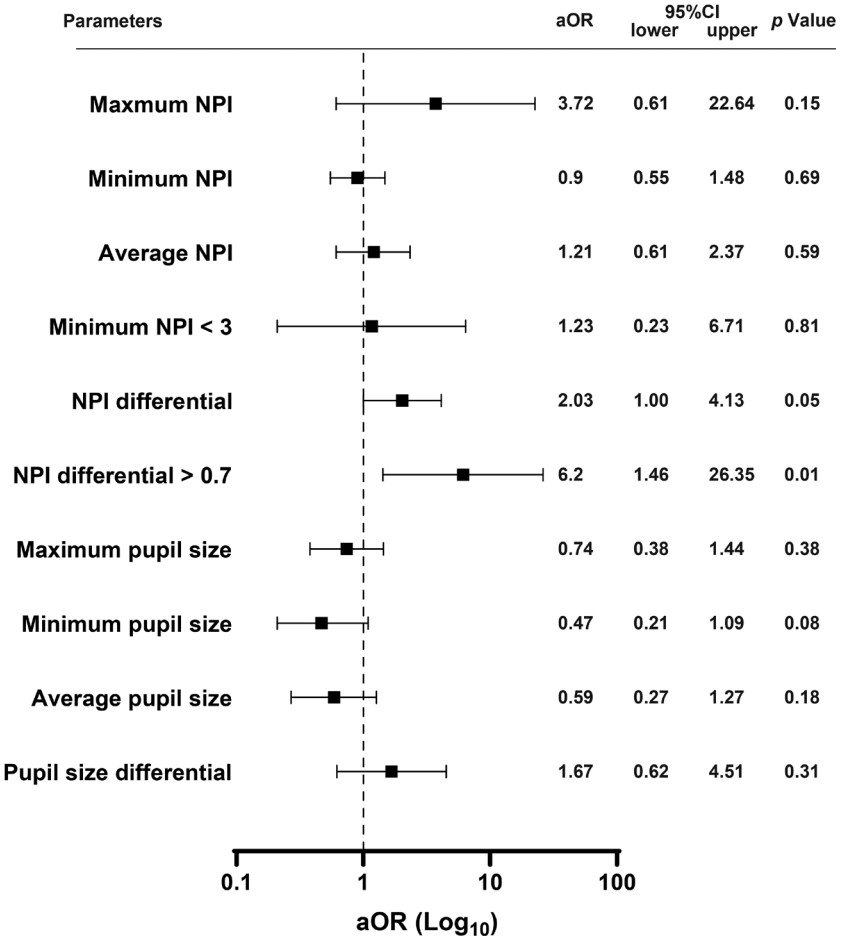


Figure 1. Multiple logistic regression analysis for predicting post-stroke delirium. Forest plot for delirium prediction. The multiple logistic regression analysis for delirium prediction was adjusted for age, sex, dementia, and the Glasgow Coma Scale score. aOR, adjusted odds ratio; CI, confidence interval; NPI, neurological pupil index.

sociated with relatively severe delirium.[10] Therefore, the NPI laterality could explain the differences observed in the light reflexes of the right and left pupils. Additionally, our study indicates that other single parameters could not elucidate this complicated process, except NPI which is calculated by combining multiple parameters concerning pupil reaction. The absence of delirium in patients with an NPI <3 may be due to severe ARAS disruption, which precludes the typical presentation of delirium.

Our study has some limitations. First, we did not investigate medication information, such as opioids, anticholinergic agents, cholinergic agents, or autonomic agents, upon admission, which could have affected the pupillary findings. Second, the algorithm used to calculate the NPI has not been publicly disclosed, thereby preventing us from fully understanding how stroke alters the NPI. Nonetheless, the NPI is based on the pupillary light reflex, and the disruption of this reflex due to stroke may play a crucial role in the observed changes.

In conclusion, our study revealed a significant association between an NPI differential >0.7 and post-stroke delirium. Notably, this biomarker was independent of dementia, indicating that pupillometry is a valuable and efficient approach for predicting delirium. Its simplicity and speed make it an effective approach for post-stroke delirium prediction.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2023.04406.

Funding statement

None

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: KT, TT, MI. Study design: KT, TT, KW, MI. Methodology: KT, TT, KK, MI. Data collection: KN, SA, RU, MM, YA, HK, RI. Investigation: KT, SA, RU. Statistical analysis: KN, TT. Writing—original draft: KN, TT. Writing—review & editing: SA, KW, SMMB, MK, KT, MI. Approval of final manuscript: all authors.

Acknowledgments

We would like to thank Editage (www.editage.com) for the English language editing.

References

1. Shaw RC, Walker G, Elliott E, Quinn TJ. Occurrence rate of delirium in acute stroke settings: systematic review and meta-analysis. *Stroke* 2019;50:3028-3036.
2. Boßelmann C, Zurloh J, Stefanou MI, Stadler V, Weber Y, Lerche H, et al. Delirium screening in aphasic patients with the Intensive Care Delirium Screening Checklist (ICDSC): a prospective cohort study. *Front Neurol* 2019;10:1198.
3. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AMJ, et al. Delirium. *Nat Rev Dis Primers* 2020;6:90.
4. Larson MD, Behrends M. Portable infrared pupillometry: a review. *Anesth Analg* 2015;120:1242-1253.
5. Miroz JP, Ben-Hamouda N, Bernini A, Romagnosi F, Bongiovanni F, Roumy A, et al. Neurological pupil index for early prognostication after venoarterial extracorporeal membrane oxygenation. *Chest* 2020;157:1167-1174.
6. Privitera CM, Neerukonda SV, Aiyagari V, Yokobori S, Puccio AM, Schneider NJ, et al. A differential of the left eye and right eye neurological pupil index is associated with discharge modified Rankin scores in neurologically injured patients. *BMC Neurol* 2022;22:273.
7. Boukrina O, Barrett AM. Disruption of the ascending arousal system and cortical attention networks in post-stroke delirium and spatial neglect. *Neurosci Biobehav Rev* 2017;83:1-10.
8. Munn BR, Müller EJ, Wainstein G, Shine JM. The ascending arousal system shapes neural dynamics to mediate awareness of cognitive states. *Nat Commun* 2021;12:6016.
9. Quadt L, Critchley H, Nagai Y. Cognition, emotion, and the central autonomic network. *Auton Neurosci* 2022;238:102948.
10. Boukrina O, Kowalczyk M, Koush Y, Kong Y, Barrett AM. Brain network dysfunction in poststroke delirium and spatial neglect: an fMRI study. *Stroke* 2022;53:930-938.

Correspondence: Tomotaka Tanaka
Department of Neurology, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan
Tel: +81-6-6170-1070
Email: tanakat@ncvc.go.jp
https://orcid.org/0000-0002-6023-236X

Co-correspondence: Masafumi Ihara
Department of Neurology, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan
Tel: +81-6-6170-1070
Email: ihara@ncvc.go.jp
https://orcid.org/0000-0002-7102-4048

Received: December 20, 2023
Revised: January 21, 2024
Accepted: January 22, 2024

https://doi.org/10.5853/jos.2023.04406

Supplementary Methods

Study design, settings, and participants

We enrolled patients who met the following criteria: successful pupil evaluation, diagnosis of ischemic stroke or intracerebral hemorrhage, and admission to the SCU of the National Cerebral and Cardiovascular Center (NCVC), Suita, Japan.

Clinical information, including age, sex, blood pressure, heart rate, medical history (hypertension, diabetes mellitus, dyslipidemia, and dementia), stroke subtypes, Glasgow Coma Scale (GCS) score, National Institutes of Health Stroke Scale score, and Intensive Care Delirium Screening Checklist (ICDSC) score, upon admission, was obtained from medical records and the NCVC Stroke Registry (ClinicalTrials.gov identifier: NCT02251665). Diagnoses were performed by board-certified neurologists, based on neurological examinations and computed tomographic and magnetic resonance imaging findings. Patients with insufficient medical records or severe optical diseases as well as those without proper NPi®-200 pupillometer evaluations in the emergency department were excluded.

In the context of the study, "successful pupil evaluation" refers to accurate and complete assessment of the pupils using an NPi®-200 pupillometer. This evaluation aimed to obtain reliable measurements of the pupillary light reflex and related parameters, such as the neurological pupil index (NPI), pupil size before and during constriction, constriction velocity (CV), dilation velocity (DV), and other relevant metrics.

Evaluation using NPi®-200

We measured the parameters of the pupils using an NPi®-200 pupillometer during treatment in the emergency department while maintaining a consistent level of brightness throughout the day. To ensure accuracy and minimize testing errors, the pupillometry was performed at least three times for each eye, and the median value of each result was analyzed. During the evaluation, an NPi®-200 pupillometer captured and analyzed the changes in pupil size and CV in response to light stimuli, thereby providing objective data on the pupillary light reflex. The parameters measured included NPI, pupil size before constriction, DV, maximum CV, latency of constriction, CV, percent change in pupil size, and pupil size at peak constriction. NPI values range from 0 to 5, and NPI values below 3 indicate an abnormal pupillary light reflex in the ipsilateral eye.[1]

To compare the bilateral pupils, we designated the largest value of each parameter as the "maximum" and the smallest value of each parameter as the "minimum." The differential of each parameter was then calculated by subtracting the minimum value from the maximum. In addition, we computed the average values of the right and left pupillary findings for each parameter.

Assessment of delirium

During their stay in the SCU, we performed daily evaluations of each patient's mental status using the ICDSC, which comprises eight items. The ICDSC is widely used with critically ill patients and those with acute stroke,[2,3] and a comprehensive explanation of this evaluation tool has been provided previously.[4] Delirium was diagnosed retrospectively by a certified neurologist when the ICDSC score equaled or exceeded 4 points.[4] However, although patients in a comatose state due to severe brain injury can score 0 points on the ICDSC, they are not classified as having delirium because they do not exhibit any manifestations of delirium.[4]

Data analysis

The data are presented as means±standard deviations or medians (interquartile range) for continuous variables and as percentages for categorical variables organized into groups of patients with and without delirium. We performed Fisher's exact or the Mann–Whitney U test to evaluate differences in the categorical or continuous variables. For continuous variables, the Mann–Whitney U test or Student's t-test was used, as appropriate. To identify the significant predictors of delirium, we constructed both univariable and multivariable logistic regression models. The multivariable model was adjusted for potential confounding factors, including age, sex, GCS score, and presence of dementia. Odds ratios with 95% confidence intervals were calculated to measure the effect size. All reported *P*-values were two-tailed, and statistical significance was defined as $P<0.05$. All statistical analyses were performed using Stata 18.0 software (StataCorp, College Station, TX, USA).

Supplementary References

1. Kim TJ, Park SH, Jeong HB, Ha EJ, Cho WS, Kang HS, et al. Neurological pupil index as an indicator of neurological worsening in large hemispheric strokes. *Neurocrit Care* 2020;33:575-581.
2. Boßelmann C, Zurloh J, Stefanou MI, Stadler V, Weber Y, Lerche H, et al. Delirium screening in aphasic patients with the Intensive Care Delirium Screening Checklist (ICDSC): a prospective cohort study. *Front Neurol* 2019;10:1198.
3. Krewulak KD, Rosgen BK, Ely EW, Stelfox HT, Fiest KM. The CAM-ICU-7 and ICDSC as measures of delirium severity in critically ill adult patients. *PLoS One* 2020;15:e0242378.
4. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001;27:859-864.

Supplementary Table 1. Comparison of pupillary findings between patients with and without delirium

	Patients without delirium (n=106)	Patients with delirium (n=25)	*P*
Maximum DV (cm/s)	0.87±0.31	0.74±0.26	0.06
Minimum DV (cm/s)	0.69±0.30	0.58±0.27	0.11
Average DV (cm/s)	0.78±0.29	0.66±0.26	0.07
DV differential (cm/s)	0.18±0.16	0.15±0.11	0.47
Maximum MCV (cm/s)	2.58±1.05	2.15±0.77	0.06
Minimum MCV (cm/s)	2.06±0.97	1.82±0.73	0.25
Average MCV (cm/s)	2.33±0.99	1.99±0.73	0.11
MCV differential (cm/s)	0.52±0.41	0.32±0.29	0.03
Maximum LAT (cm/s)	0.27±0.04	0.28±0.04	0.33
Minimum LAT (cm/s)	0.25±0.03	0.24±0.03	0.53
Average LAT (cm/s)	0.26±0.03	0.26±0.03	0.75
LAT differential (cm/s)	0.02±0.02	0.03±0.05	0.04
Maximum CV (cm/s)	1.81±0.75	1.50±0.58	0.06
Minimum CV (cm/s)	1.44±0.73	1.21±0.57	0.15
Average CV (cm/s)	1.63±0.73	1.36±0.56	0.08
CV differential (cm/s)	0.37±0.30	0.29±0.23	0.21
Maximum %CH (%)	25.60±7.40	23.84±5.63	0.27
Minimum %CH (%)	21.61±8.05	18.70±6.99	0.10
Average %CH (%)	23.67±7.55	21.27±5.96	0.14
%CH differential (%)	4.00±3.40	5.14±4.36	0.15
Maximum pupil size at peak constriction (mm)	2.42±0.56	2.54±0.59	0.34
Minimum pupil size at peak constriction (mm)	2.21±0.40	2.08±0.40	0.13
Average pupil size at peak constriction (mm)	2.31±0.45	2.31±0.44	0.98
Pupil size differential at peak constriction (mm)	0.20±0.36	0.46±0.48	<0.01

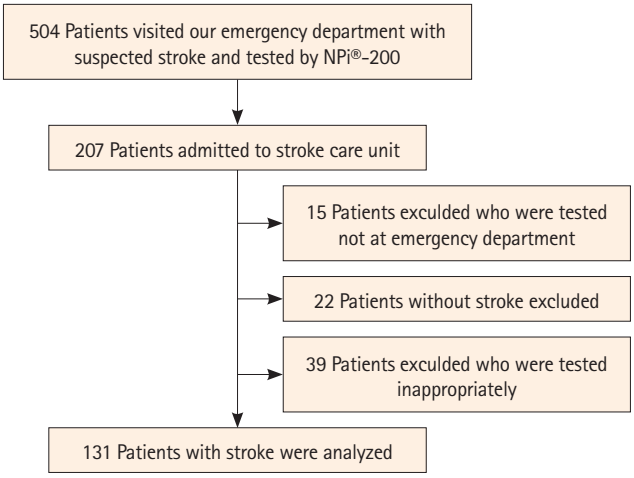
Values are presented as mean±standard deviation.
DV, dilation velocity; MCV, maximum constriction velocity; LAT, latency of constriction; CV, constriction velocity; %CH, percent change in pupil size.

Supplementary Table 2. Multiple logistic regression analysis for predicting post-stroke delirium

	Adjusted odds ratio	95% CI	*P*
MCV differential (cm/s)	0.21	0.04–1.05	0.06
LAT differential (cm/s)	1.67×10^{6}	0.17–N/A	0.08
Pupil size differential at peak constriction (mm)	2.44	0.85–7.03	0.10

Adjusted by age, sex, Glasgow Coma Scale score, and presence of dementia.
CI, confidential interval; MCV, maximum constriction velocity; LAT, latency of constriction; N/A, not applicable.

https://doi.org/10.5853/jos.2023.04406



Supplementary Figure 1. Flowchart. Between April 2022 and October 2022, 504 patients with suspected stroke were admitted to our hospital and underwent NPi®-200 pupillometry testing, and 207 patients were admitted to the stroke care unit. Among them, 39 patients who underwent NPi®-200 pupillometry less than three times for each eye were excluded. After excluding 22 patients without stroke, 131 patients with successful pupil evaluations were analyzed.