

## Supratentorial intracerebral hemorrhage volume and other CT variables predict the neurological pupil index

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### ABSTRACT

**Objectives:** There is growing interest in the ability of automated infrared pupillometry to assess severity of neurological illness. We studied the correlation between computed tomography (CT) indicators of intracerebral hemorrhage (ICH) severity with objective measures of the pupillary light reflex (PLR), and hypothesized that hemorrhage volume would predict the Neurological Pupil index™ (NPI™), an indicator of pupillary reactivity. **Methods:** This study examined data from patients with supratentorial ICH who underwent serial pupillometer evaluations. CT images were examined to determine the location and laterality of the hemorrhage, along with hematoma volume (using the simplified ABC/2 method), midline shift, hydrocephalus score, and modified Graeb score (indicating interventricular hemorrhage). Demographics were examined with standard measures of central tendency, hypotheses with logistic regression, categorical data with Fisher's Exact X2, and multivariate modeling with constructed MAX-R models.

**Results:** Data were gathered from 44 subjects. ICH volume exhibited the strongest correlation with NPi (ipsilateral [ $r^2 = 0.48$ ,  $p < 0.0001$ , contralateral [ $r^2 = 0.39$ ,  $p < 0.0001$ ]). Horizontal midline shift of the septum pellucidum also correlated with NPi (ipsilateral [ $r^2 = 0.25$ ,  $p = 0.0006$ ], contralateral [ $r^2 = 0.15$ ,  $p = 0.0106$ ]), as did shift of the pineal gland (ipsilateral [ $r^2 = 0.21$ ,  $p = 0.0017$ ], contralateral [ $r^2 = 0.11$ ,  $p = 0.0328$ ]). ICH volume was the most predictive of abnormal NPi (AUC = 0.85 for ipsilateral and 0.88 for contralateral NPi), and multivariate modeling identified additional independent predictors of NPi.

**Conclusion:** ICH volume and shift of midline structures correlate with NPi, and abnormalities in NPi can be predicted by hematoma volume and other CT indicators of ICH severity. Future studies should explore the role of NPi in detecting early hematoma expansion and worsening midline shift.

### 1. Introduction

Intracerebral hemorrhage (ICH) results from nontraumatic bleeding into the brain parenchyma [1] and constitutes a tenth of all stroke cases [2–4] with an incidence of > 40,000 per year in the United States. [5]. Hemorrhage expansion, an important predictor of outcome after ICH, can occur within an hour of onset [6], continue for up to 36 h, and result in rapid neurological deterioration [7,8]. It has been estimated that more than 70 % of patients with an ICH who present within three hours of symptom onset have evidence of hematoma expansion at 24 hs and hematoma growth is an independent determinant of mortality and

functional outcome after ICH. [9]. Therefore, hematoma growth is an important target for therapeutic intervention. Currently, non-contrast computed tomography (CT) imaging is the principal method for diagnosing ICH as well for detecting hematoma expansion. CT scans can also be used to analyze other factors that have been shown to predict poor outcome and indicate ICH severity. These factors include hematoma size, volume, and location, along with shift of midline structures, intraventricular hemorrhage (IVH), and accompanying hydrocephalus [10–12]. However, it is not practical to obtain repeated serial CT scans in ICH patients to assess for these factors. A noninvasive indicator method of assessing the aforementioned factors would be very useful

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and could serve as a trigger for repeating a CT scan in a patient with ICH.

Serial bedside assessment of ICH patients include neurologic assessments including the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS), while the ICH Score is used initially to determine baseline severity. A key piece of a neurological exam is the pupillary assessment, which examines the size, shape, symmetry, and reactivity of the pupils [13]. Assessment of the pupillary light reflex (PLR) provides information about the functionality of the optic and oculomotor nerves and can indicate the degree of neurological injury [14], increase in intracranial pressure, and presence of herniation [15,16]. An abnormal PLR or sudden change in pupil functionality or presentation can indicate a medical emergency, and as abnormal pupillary assessments are correlated to poor outcomes, accuracy and communication of this information is essential [17]. The traditional method of conducting pupillary assessments- a manual exam in which the examiner uses a light source to assess pupil reactivity and a pupil gauge to determine pupil size- has low interrater reliability [18,19]. To address the need for standardized pupillary assessment, handheld automated infrared pupillometry (subsequently referred to as pupillometry) devices are becoming popular for use at the bedside of neurocritical patients [20]. Pupillometers provide quick and objective measurements of many measures of the PLR, such the pupil size, constriction and dilation velocity and latency. In addition, the NeuroOptics NPi-200 pupillometer also measures the Neurological Pupil Index (NPI), which is a proprietary algorithm where a patient's pupillary parameters are compared to a normative pupil response to light and graded on a scale of 0–5. A value less than 3 is considered abnormal and a value of 0 indicates a pupil that does not react to light [21,22].

The relation between measurements obtained by pupillometry and severity of several acute neurological conditions is a growing area of study [23–25]. Osman et al. [26] found that, in stroke patients, horizontal shift of the septum pellucidum correlates with the NPI, the pupil constriction velocity, and pupillary asymmetry. Other authors have observed that in patients with aneurysmal subarachnoid hemorrhage,

**Table 1**  
Baseline characteristics.

<b>Mean Age in years</b>	65.4 (15.2)		
<b>Gender</b>	Female	Male	
	22 (50%)	22 (50%)	
<b>Race</b>	White	African American/Black	
	30 (68.2 %)	8 (18.2 %)	
	Asian	Other/Unknown 2 (4.6 %)	
	4 (9.1 %)		
<b>ICH Etiology</b>	Amyloid	Arterial/ Venous Malformation	Coagulopathy/ Anticoagulation
	4 (9.1 %)	3 (6.8 %)	2 (4.6 %)
	Hemorrhagic	Hypertension	Other/Unknown
	Conversion of Ischemic Stroke	26 (59.1 %)	5 (11.4 %)
<b>ICH Location</b>	Basal Ganglia/Thalamus	Lobar	
	25 (56.8 %)	19 (43.2 %)	
<b>ICH Laterality</b>	Left	Right	
	18 (40.9 %)	26 (59.1 %)	
<b>Time between Onset and PR (hours)†</b>	38.7 (42.8) Range: 3.17–172	<b>Time between CT Scan and PR (hours)</b>	2.8 (1.7) Range: 0.27–6.08
		<b>NIHSS Score</b>	16.6 (11.0)
<b>GCS Score</b>	10.6 (4.3)	<b>ICH Volume (mL)</b>	47.2 (54.1)
<b>ICH Score</b>	2.0 (1.4)	<b>SP Shift (mm)</b>	6.4 (6.0)
<b>PG Shift (mm)</b>	2.6 (3.2)	<b>mGS</b>	9.5 (8.5)
<b>HCS</b>	5.6 (3.6)	<b>Abnormal for Ipsi. NPI</b>	7 (15.9 %)
<b>Ipsi. NPI</b>	7 (15.9 %)	<b>Contra. NPI†</b>	5 (11.6 %)

PR is pupillometry reading, PG is pineal gland, SP is septum pellucidum, and HCS is hydrocephalus score.

†Not available for 1 of the 44 subjects.

the NPI was lower in patients with more severe manifestations of the disease and unfavorable outcomes [27–29]. Pupillometry has also been shown to hold prognostic value for patients with cardiac arrest and acute brain lesions [30]. A fast, reliable, and simple method to monitor neurological condition would provide great benefit to the care of ICH patients. The purpose of this study was to investigate the relation between the NPI and CT scan markers of hemorrhage severity in supratentorial ICH patients.

## 2. Methods

This was a retrospective analysis of prospectively collected data. We analyzed head CT scans and pupillometry data from ICH patients in the Establishing Normative Data for Pupillometer Assessment in Neuroscience Intensive Care (END-PANIC) registry (NCT02804438) [31]. The first pupillometry reading within 6 h of a CT scan was selected. The electronic medical record (EMR) was also reviewed to determine ICH etiology and time of onset (the time last known well was used when the time of onset was not recorded). Patient demographics, GCS score, NIHSS score, and the ICH Score closest to the time of the selected pupillometry reading were also recorded.

The END-PANIC registry enrolls patients who receive pupillometry assessments as part of their standard of care at one of four neurocritical care units located in the US [31,32]. An NPi-200 Pupillometer by NeuroOptics is used to obtain measurements of the PLR and derive the NPI. These values are stored in the patient's SmartGuard® device, from which the data is transferred to an EMR. The pupillometry data is then abstracted from the EMR into an electronic spreadsheet and incorporated into the END-PANIC database. This study only used data from patients admitted to the neurocritical care unit at the primary investigating institution between October 2015 and August 2018.

### 2.1. Analysis of CTs from ICH patients

Non-contrast head CT scans from patients with supratentorial ICH were examined to measure the ICH size, calculate the ICH volume, and evaluate the degree of hydrocephalus, IVH, and mass effect. The laterality and location of the ICH, deep (basal ganglia/thalamus) or lobar, were also recorded. Patients who did not have a pupillometry reading with 6 h of a head CT scan were excluded. Patients were also excluded if they had multiple areas of ICH, significant subarachnoid hemorrhage, another independently arising lesion in the brain, or an artifact on their CT scans that interfered with analysis. Additionally, patients were also excluded if the earliest pupillometry reading was taken after hematoma evacuation or decompressive craniectomy. It was confirmed that no ventriculostomy procedure had been performed between the time of the pupillometry reading and time of the head CT scan, although some patients had a ventricular drainage catheter placed before both the reading and the scan.

The ICH volume was calculated by using the ABC/2 method first described by Kwak et al., which approximates the volume of the hematoma to that of an ellipse and is a simplification of the  $(4\pi/3)(l \cdot w \cdot h/8)$  formula for the volume of an ellipse [11]. The length, A, is the longest diameter of the hemorrhage on the CT slice on which the area of ICH is the largest. The width, B, is the longest diameter perpendicular to A on the same CT slice as A. The height, C, is the product of the number of CT slices on which the ICH is visible and the thickness of each slice.

The degree of mass effect due to the hemorrhage was determined by measuring the horizontal displacement of the pineal gland and septum pellucidum, which are midline structures. The degree of ventricular enlargement was evaluated using the hydrocephalus scoring system developed by Diringer et al. [10] The degree of intraventricular hemorrhage was determined by using the Modified Graeb Score (mGS) developed by Morgan and Dawson et al. [12].

**Table 2**  
Correlation between Variables.

	P-value IPSI. NPi	r <sup>2</sup>	P-value CONTRA. NPi	r <sup>2</sup>
ICH VOLUME	<0.0001	0.48	<0.0001	0.39
SP SHIFT	0.0006	0.25	0.0106	0.15
PG SHIFT	0.0017	0.21	0.0328	0.11
HCS	0.7852	0.002	0.6077	0.007
mGS	0.4813	0.01	0.2472	0.03
	SP SHIFT		PG SHIFT	
ICH VOLUME	<0.0001	0.47	0.0105	0.15

Non-adjusted r<sup>2</sup> is shown. Ipsi. and contra. represent the pupils ipsilateral and contralateral to the ICH.

## 2.2. Statistical analysis

Analyses were performed using SAS 9.4 for Windows. Descriptive statistics were performed on baseline characteristics, such as demographics (age, race, and gender) and certain characteristics of the hemorrhage (location, laterality, and etiology). Values are presented as mean (standard deviation) or frequency (percent) unless otherwise indicated. Univariate linear regression was used to analyze the association between the CT variables and NPi. Multivariable analysis using MAX-R models was performed to identify independent predictors of NPi. A logistic regression of a binary response variable “1” for normal NPi versus “0” for abnormal NPi on the independent variable ICH volume with a sample size of 44 observations achieves 80 % power at a 5 % significance level to detect a fifty per cent change in the probability of normal NPi.

## 3. Results

Of the 103 patients in the END-PANIC registry with a history of supratentorial ICH, 59 were excluded (28 did not have pupillometry within 6 h of a CT scan, 4 had hematoma evacuation prior to pupillometry, 9 had multiple hematoma, 3 had significant subarachnoid hemorrhage, 2 had arteriovenous malformations, 2 had artefacts hindering volumetry, 2 had decompressive hemicraniectomy and 1 had a hemorrhage related to a ventricular shunt). Of the 44 patients with supratentorial ICH included in this study, the average age was 65.4 (15.2) years, the gender distribution was 22 (50 %) male and 22 (50 %) female, and racial distribution was 68.2 % White, 18.2 % African American or Black, and 9.1 % Asian (Table 1). The primary etiology for ICH was hypertension (59.1 %), the mean GCS was 10.6 (4.3), the mean NIHSS score was 16.6 (11.0), and the mean ICH Score was 2.0 (1.4). The average number of hours between symptom onset and time of the pupillometry reading was 38.7 (42.8). The average number of hours between time of the CT scan and time of the pupillometry reading was 2.8 (1.7). The ICH was in the basal ganglia or thalamus for 56.8 % of the patients and in one of the cerebral lobes for 43.2 % (on the left side for 40.9 % and on the right for 59.1 %). The factors which correlated with the NPi were the total volume of ICH and the horizontal displacement of midline structures (Table 2). We did not find statistically significant correlations between NPi and measures of interventricular hemorrhage or hydrocephalus.

### 3.1. ICH volume

The mean total volume of hemorrhage was 47.2 (54.1) mL. There was a correlation between ICH volume and the NPi of the pupil ipsilateral (r<sup>2</sup> = 0.48, p < 0.0001) and contralateral (r<sup>2</sup> = 0.39, p < 0.0001) to the hematoma (Fig. 1). ICH volume was the most predictive of abnormal NPi; the area under the ROC curve was 0.85 for ipsilateral and 0.88 for contralateral NPi (Fig. 2). Linear regression modeling showed strong correlation between the total volume of ICH and the estimated probability of an abnormal ipsilateral NPi (r<sup>2</sup> = 0.95, p < 0.0001,) and

contralateral NPi (r<sup>2</sup> = 0.92, p < 0.0001). However, the estimated probability of an abnormal ipsilateral or contralateral NPi only exceeds 50 % at large ICH volumes (approximately 150 mL).

### 3.2. Midline shift of pineal gland and septum pellucidum

The mean horizontal shift of the pineal gland was 2.6 (3.2) mm. The shift was less than 3 mm in most cases (66 %), 3 to < 6 mm for 23 %, 6 to < 8 mm for 5 %, and greater than 8 mm for 7%. There was a correlation between shift of the pineal gland and NPi of the ipsilateral (r<sup>2</sup> = 0.21; p = 0.0017) and contralateral (r<sup>2</sup> = 0.11; p = 0.0328,) pupils. There was a significant correlation between pineal gland shift and the ICH volume (r<sup>2</sup> = 0.38; p = 0.0105). Pineal gland shift was not highly predictive of NPi; the area under the ROC curve was 0.60 for ipsilateral and 0.61 for contralateral NPi.

The mean horizontal shift of the septum pellucidum was 6.4 (6.0) mm. The shift was less than 3 mm for 34 % of cases, 3 to < 8 mm for 34 %, 8 to < 13 mm for 14 %, and greater than 13 mm for 18 %. There was a correlation between shift of the septum pellucidum and NPi of the ipsilateral (r<sup>2</sup> = 0.25; p = 0.0006) and contralateral (r<sup>2</sup> = 0.15, p = 0.0106) pupils. There was a significant correlation between septum pellucidum shift and ICH volume (r<sup>2</sup> = 0.69; p < 0.0001). Septum pellucidum shift was fairly predictive of NPi; the area under the ROC curve was 0.71 for ipsilateral and 0.72 for contralateral NPi. Linear regression modeling showed strong correlation between the septum pellucidum shift and the estimated probability of an abnormal ipsilateral NPi (r<sup>2</sup> = 0.96; p < 0.0001) and contralateral NPi (r<sup>2</sup> = 0.93; p < 0.0001). However, the estimated probability of an abnormal ipsilateral or contralateral NPi did not exceed 50 % for the range of septum pellucidum shift observed in this study.

### 3.3. Multivariate analysis

Multivariate (MAX-R) analysis modeling contributions of the ICH volume, septum pellucidum shift, pineal gland shift, hydrocephalus score, modified Graeb Score, and location to NPi revealed that for both ipsilateral and contralateral NPi, the best 1-variable model was that which included the ICH volume (R<sup>2</sup> = 0.4791 for ipsilateral and 0.3895 for contralateral NPi). For ipsilateral NPi, the best model- in which Mallows' Cp value was the lowest- was a 3-variable one including the ICH volume, location, and pineal gland shift (R<sup>2</sup> = 0.5739 and Cp = 4.5759; Table 3). For contralateral NPi, the best model was a 5-variable one including the ICH volume, septum pellucidum shift, pineal gland shift, mGS, and location (R<sup>2</sup> = 0.5197 and Cp = 5.0003).

## 4. Discussion

The results of this study show that ICH volume correlates with the NPi values obtained from patients with supratentorial ICH. Furthermore, ICH volume was found to account for approximately 40 % of the variation in NPi. Among the factors associated with ICH severity that were studied, ICH volume exhibited the highest predictive value for abnormal NPi. There was no difference between the ability of ICH volume to predict ipsilateral and contralateral NPi. While the results do not infer a causal relationship, these findings suggest that ICH volume may be one of the most important variables for indicating abnormalities in the PLR, in supratentorial ICH patients. It should be noted that the estimated probability of an abnormal NPi was found to exceed 50 % at very high ICH volumes (those over approximately 150 mL), found in only 4 of 44 subjects. This diminishes the clinical utility of the NPi as a routine monitoring tool in these patients as one would assume that routine clinical examination including the GCS and/or the NIHSS could detect hematoma expansion to this degree as well. However, in instances where the patient is deeply sedated or pharmacologically paralyzed to facilitate mechanical ventilation or management of raised intracranial pressure, the GCS and NIHSS scores could be confounded and

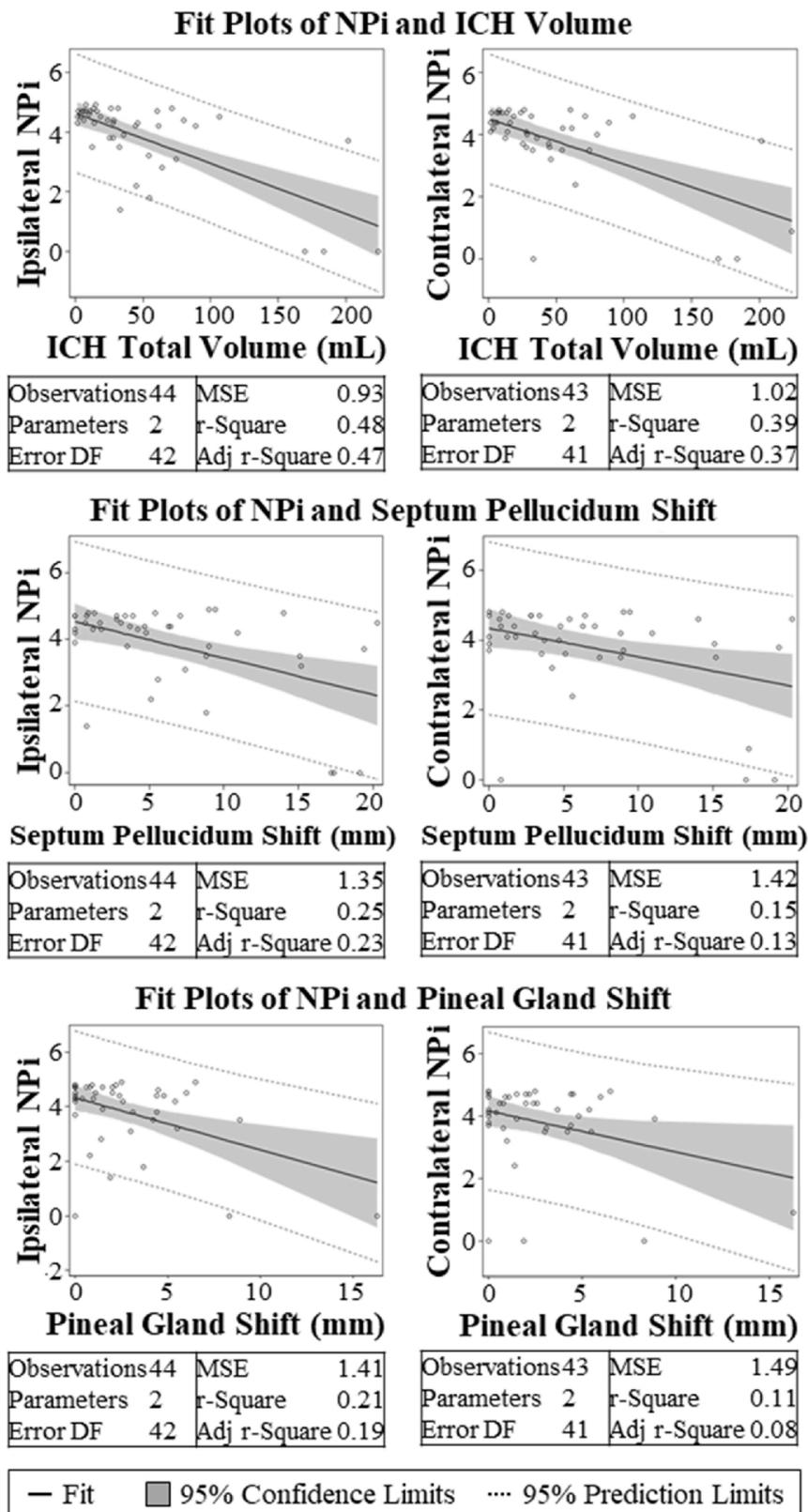


Fig. 1. Linear Regression Models of NPi and CT Variables.

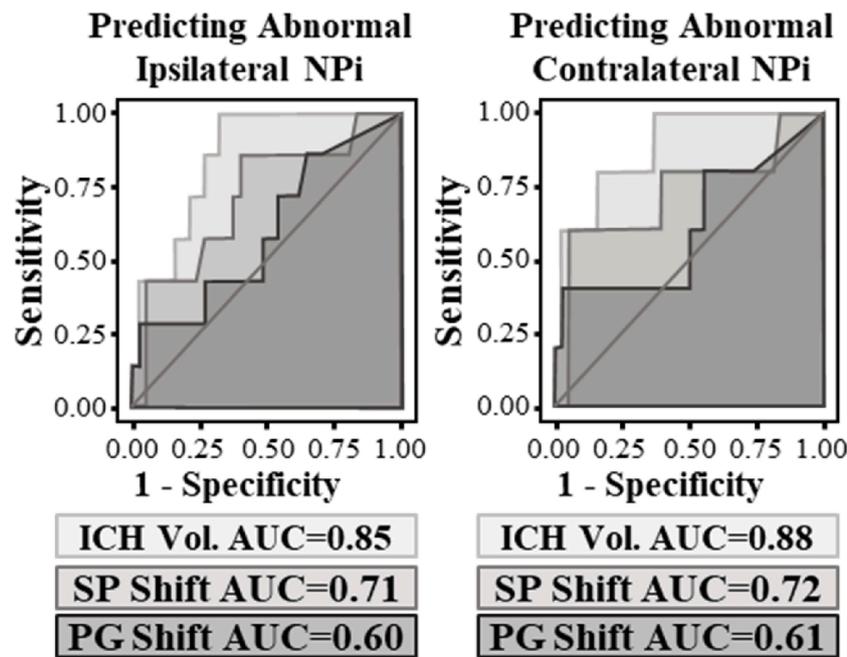


Fig. 2. ROC Curves Modeling Prediction of Abnormal NPi with CT Variables. SP is septum pellucidum and PG is pineal gland.

Table 3  
Multivariate Model of NPi.

	Variables	Parameter Estimate	Standard Error	P-value
IPSI. NPi	Intercept	6.502	0.745	<.0001
	ICH Volume	-0.017	0.004	<.0001
	PG Shift	-0.164	0.056	0.006
	Location	-0.627	0.290	0.037
	Intercept	6.051	0.792	<.0001
CONTRA. NPi	ICH Volume	-0.018	0.004	<.0001
	mGS	-0.046	0.019	0.022
	SP Shift	0.087	0.043	0.048
	PG Shift	-0.121	0.051	0.048
	Location	-0.499	0.312	0.119

monitoring the NPi may be helpful. The computed delta NPi for ICH volume increase in our study was 0.54. The results of this study are limited by its sample size and it is possible that we would be able to clarify other patterns between ICH volume and NPi with a larger sample.

Although subjective assessment of PLR does not correlate with midline shift, prior studies have found that midline shift does correlate with NPi and accounts for some of the variance observed in the NPi [26, 33,34]. Although septum pellucidum shift exhibited predictive value for NPi, multivariate analysis showed that it was not an independent predictor of ipsilateral NPi. The strong correlation between ipsilateral NPi and septum pellucidum shift may be due to its dependence on ICH volume, which may act as a confounding variable in that relationship (Table 2). Pineal gland shift, on the other hand, was found to be an independent predictor of both ipsilateral and contralateral NPi. ICH volume also correlated more strongly with septum pellucidum shift than with pineal gland shift, and it is possible that ICH volume affects septum pellucidum shift more than pineal gland shift and is responsible for the difference in these two midline structures' correlations with and predictive value for NPi to some degree.

Other variables also showed independent predictive value for NPi in the multivariable analysis (Fig. 3). Location, categorized as either deep (basal ganglia or thalamus) or lobar, was an independent predictor for ipsilateral NPi. Although a correlation between mGS and either

ipsilateral or contralateral NPi was not found, mGS was shown to be an independent predictor for contralateral NPi. Among the variables that were found to correlate with NPi, the correlation was stronger with the NPi of the pupil ipsilateral to the hematoma than with the contralateral NPi.

4.1. Limitations

Our study would have been more robust with a larger sample size. A large number of patients with ICH were excluded due to lack of a pupillometry reading within six hours of a head CT scan, lack of a pupillometry reading before the brain tissue containing the hemorrhage was removed, presence of multiple areas of ICH, or presence of significant subarachnoid hemorrhage, and other complications.

5. Conclusion

The NPi correlates with ICH volume and shift of midline structures, and the hematoma volume is the strongest predictor of NPi among the CT variables studied. Pineal gland shift, location, septum pellucidum shift, and mGS also showed independent predictive value with multivariable modeling. Differences between the ipsilateral and contralateral pupils were observed, with the ipsilateral NPi exhibiting higher correlation with hematoma volume and midline shift, and different multivariable models for the prediction of NPi. As the END-PANIC database continues to grow, we hope to conduct additional studies on this subject with larger sample sizes. Future studies on the role of NPi in detecting hematoma expansion and worsening midline shift would further elucidate the utility of pupillometry in assessing the degree of neurological deterioration in intracerebral hemorrhage patients.

CRediT authorship contribution statement

Khadijah Mazhar: Writing - original draft, Investigation, Visualization, Formal analysis. DaiWai M. Olson: Methodology, Resources, Supervision, Writing - review & editing, Funding acquisition. Folefac D. Atem: Software, Formal analysis, Data curation, Writing - review &

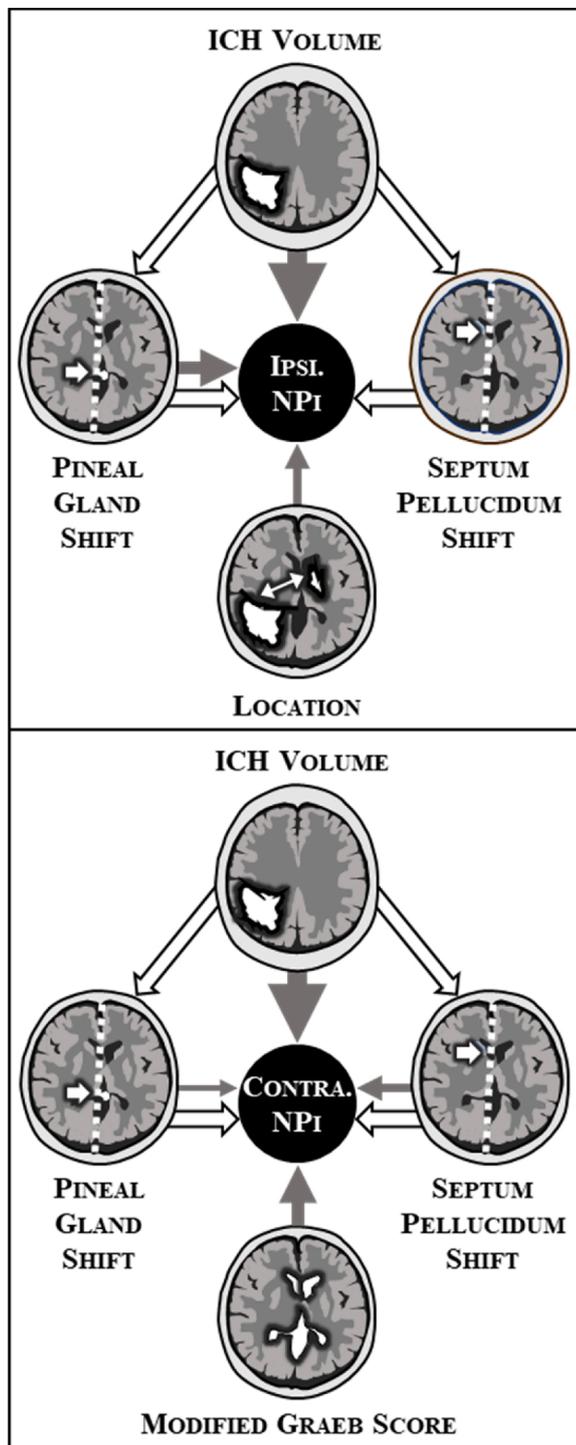


Fig. 3. Independent Predictors of NPi.

White arrows denote correlation. Grey arrows indicate independent predictors of NPi.

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