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Contribution of pupillary light reflex assessment to Glasgow Coma Scale for prognostication in patients with traumatic brain injury

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ORIGINAL ARTICLE

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Background: Glasgow Coma Scale (GCS) and the pupillary light reflex (PLR) are important prognostic tools for traumatic brain injury (TBI). This study compared the predictability of GCS, GCS plus manual PLR (GCS-P), GCS plus Neurological Pupil index (GCS-NPi), and average NPi (avgNPi) in predicting discharge outcome in patients diagnosed with TBI.
Methods: Data were obtained from a multicenter prospective registry that included 175 subjects with TBI. A nonlinear mixed model (NLMIXED) approach was used to determine which of the following independent variables (GCS, GCS-P, GCS-NPi, and avgNPi) is a better predictor of modified Rankin Scale (mRS) at discharge by fitting four predictive models for comparison.
Results: The NLMIXED model for longitudinal data determined that GCS, GCS-P, GCS-NPi, and avgNPi were all significant predictors of mRS at discharge (P<0.001). Age was a significant predictor of the discharge mRS (P<0.001). There was a strong significant correlation between the four predicting variables (P<0.05). The maximum likelihood estimation (MLE) of GCS was –0.17 (P<0.001), MLE of GCS-P was –0.17 (P<0.001), MLE of GCS-NPi was –0.17 (P<0.001), and the MLE of avgNPi was –0.39 (P<0.001).
Conclusion: Our findings suggest that any of the four variables (GCS, GCS-P, GCS-NPi, and avgNPi) could be used as a potential predictor of discharge mRS in a patient with TBI. This warrants future investigations to explore the combination of pupillary reactivity scores and NPi with GCS for prognostication in patients with TBI.

Keywords: Pupil; Pupil disorders; Reflex, Pupillary; Critical illness; Traumatic brain injury

INTRODUCTION

Patients with traumatic brain injury (TBI) experience several methodological challenges related to outcome assessment due to the limited availability of prognostic tools for predicting outcomes. The Glasgow Coma Scale (GCS) was developed as a tool to assess the "depth and duration of impaired consciousness and coma [1]." Although, GCS is the most widely used prognostic tool for predicting outcomes in patients with TBI, the availability of other online prognostic calculators such as the international

mission for prognosis and clinical trials in traumatic brain injury (IMPACT) and corticoid randomisation after significant head injury (CRASH) prognostic models may also aid in estimating the 6-month outcomes in patients with moderate to severe TBI in addition to providing support to decision making and clinical judgment for determining the treatment goals and care in TBI [2,3]. In 2014, Teasdale et al. [4] cautioned that the GCS should not be used as a prognostic instrument except when used in conjunction with multivariate modeling. The development of the international Curing Coma Campaign heralds a renewed interest in prognostication and assessment of patients with disorders of consciousness [5]. The most recent adaption to the GCS, the GCS-pupil (GCS-P) adjusts for findings based on a subjective assessment of the pupillary light reflex (PLR). However, both the GCS and GCS-P predate the adoption of automated infrared pupillometry (AIP) [6-8]. Therefore, the purpose of this study is to explore the contribution of PLR assessment to prognostication in patients with TBI.

The rates of unfavorable outcomes after TBI can exceed 20%, and up to 15% of TBI patients with mild injury will have post-concussive symptoms [9,10]. Prevention of secondary brain injury relies heavily upon the ability to provide an accurate assessment of the patient at baseline, and subsequent serial assessments [11,12]. The GCS evaluates three components of responsiveness (eye-opening, motor, and verbal responses) [13]. Each component is evaluated and scored separately; component scores are then summed; ranging from 3 to 15 (higher scores represent the best responsiveness). The PLR has been examined both historically, and recently, as a prognostic variable of both morbidity and mortality [14-16]. Previous work by Perel et al. [3], Marmarou et al. [2], and Brennan et al. [17] suggest that a combination of GCS and PLR may serve as good predictors to predict outcome in patients with TBI.

Traditionally, the PLR was a subjective assessment performed using a flashlight or penlight. This method of assessment has been found to be unreliable and imprecise [18,19]. The PLR is a summary assessment that begins by evaluating the size of the pupil at rest, providing a light stimulus, and observing the degree to which the pupil constricts in response to that stimulus [20]. AIP is an emerging technology that has high reliability, precision, and reproducibility as compared to the standard pen-light examination to examine the pupillary response. It provides an objective measurement of pupillary size, symmetry, and reactivity to light [20]. The assessment of PLR by pupillometry has recently emerged as a useful tool for assessing pupillary reactivity and triaging patients for expediting care in patients with neurological diseases [21]. The NPi-200 pupilometer assesses pupillary reactivity and provides a summary score called the Neurological Pupil index (NPi) [22]. The NPi is a standardized way to assess the PLR using a hand-held pupilometer. Values range from 0 to 5 (NPi $\geq$ 3.0 is considered normal, and $<$ 3.0 is considered abnormal). Even though recent literature has indicated the usefulness of pupillometry due to its high accuracy and reliability, there is a lack of research to determine the usefulness of NPi in combination with GCS score for predicting outcome in patients with TBI.

In patients with TBI, the modified Rankin Scale (mRS) has been used to assess the degree of disability by providing a score, ranging from 0 (fully independent) to 6 (dead) to determine the functional outcome in patients [23,24]. Even though GCS is a simple and powerful prognostic tool, it has its limitations as an independent prediction tool of mortality and unfavorable outcomes [2,17,25]. Previous studies have combined GCS with PLR to predict the functional outcome in patients with TBI. But, to our knowledge, no study has examined the predictive ability of GCS in combination with NPi, or using NPi alone to predict mRS outcome in patients with TBI.

METHODS

The Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (ENDPANIC) registry is a multi-center international registry of pupillary assessments and acute care data points (NCT02804438). The registry was open in 2014; a full report of the methods and additional data can be found in a previous publication [26]. Data were obtained from 175 adults (over 18 years of age) patients diagnosed with TBI who had admission GCS and AIP data linked to discharge mRS. PLR analysis was done via commercial pupilometer (NPi 200; Neuroptics Inc., Irvine, CA, USA). Pupillometry was performed and pupillometry data were collected throughout the patients' hospital stay, based on the frequency of neurological assessments ordered by the physician. This is usually every hour for the first few days, with the interval being increased subsequently once the patient is felt to be neurologically stable and not at a high risk of neurological deterioration. Data on demographic characteristics and length of hospital and ICU stay were obtained from the registry. For the GCS-P, pupillary reactivity was derived by the AIP values wherein, an NPi of 0 was scored as non-reactive and an NPi value above 0 was scored as reactive. In this manner, the GCS-P score (range, 1–15) was derived by subtracting the number of non-reactive pupils (0, 1, or 2) from the GCS (range, 3–15) [17]. Discharge mRS scores were abstracted from the discharge notes in the electronic medical record as assessed by the discharge therapist and/or physician.

The GCS-NPi score (range, 1–15) was created by subtracting points from the GCS based on NPi. We subtracted 0 points if the

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NPi of both eyes was > 3.0; and subtracted 0.5 point if the NPi of one eye was > 3.0 and the other eye was 0.1–2.9; subtracted 1 point if the NPi of both eyes was between 0.1 and 2.9; subtracted 1.5 points if NPi of one eye was between 0.1 and 2.9 and the other eye NPi was 0; and subtracted 2 points if the NPi of both eyes was 0. The NPi values from the left and right eye were summed and divided by 2 to provide the average NPi (avgNPi).

Statistical analysis

Summary statistics and statistical models were developed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). Patient characteristics such as age, sex, race, and ethnicity were summarized at baseline. The continuous variables such as age and avgNPi were summarized as mean and standard deviation while categorical variables such as sex, ethnicity, race, PLR response, were described as frequencies and percentages. Ordinal variables were described using median and interquartile range (IQR).

To ascertain which of the measures (GCS, GCS-P, GCS-NPi, or avgNPi) is a better predictor of mRS, four separate predictive models were fitted. Because the relationship between mRS and each predictor is unlikely to be linear, and also, to take into consideration the repeated nature of the data, a random effect nonlinear mixed model (NLMIXED) was fitted for each of the potential predicting variables of mRS [27,28]. This model was fitted after the proportional odd assumption of ordinal logistic regression was violated [29]. Even though this model does not assume a linear relationship between the dependent and independent variable, both models take the dependency between observations based on the same cluster repeated measure per subject into account by introducing one or more random effects. This procedure fits multiple models by identifying the maximum likelihood estimation (MLE) and maximizing the approximate integrated likelihood by adaptive Gauss-Hermite quadrature. In this model, we controlled for age analyzed as a continuous confounder, sex analyzed as a binary confounder, and ethnicity as a binary predictor. A similar NLMIXED was employed to compute the correlation matrix for each of the four predictors.

RESULTS

One hundred seventy-five subjects met inclusion criteria. As shown in Table 1, the majority of the patients were male (n = 116, 66.29%), White (n = 102, 58.29%) and non-Hispanic (n = 164, 93.71%). The mean (standard deviation [SD]) was 56.4 years (22.3) for age, 6.8 days (7.7) for ICU length of stay, and 16.4 days (24.1) for hospital length of stay. The median (IQR) was 13 (6–15) for GCS, 12 (6–15) for GCS-P, and 12 (6–14.5) for GCS-NPi. The mean (SD) was 3.74 (0.11) for the left eye, 3.72 (0.11) for the right eye, and 3.73 (1.31) for the left and right eye averaged together (avgNPi). Of 175 patients, 158 patients (90.3%) had both pupils reactive. The median (IQR) was 4 (2–5) for discharge mRS (where an mRS of 0 indicated that the patient was absent of neurological symptoms).

Of the 175 patients, 149 (85.14%) survived and 26 (14.86%) died (mRS = 6). Table 2 displays the calculated MLE, standard error, 95% confidence interval (CI), and P-value for the four parameters; GCS, GCS-P, GCS-NPi, and avgNPi and for the covariates (age, sex, and ethnicity) in the NLMIXED model procedure after successful convergence. The MLE (95% CI) of total GCS was –0.17 (–0.22 to –0.12, $P < 0.001$), for GCS-P was –0.17 (–0.22 to –0.12, $P < 0.001$), for GCS-NPi was –0.17 (–0.22 to–0.12,

Table 1. Patient baseline characteristics

Variable	Value (n=175)
Age (yr)	56.41±22.3
Sex	
Male	116 (66.29)
Female	59 (33.71)
Race	
African American	3 (1.71)
Asian	61 (34.86)
Caucasian	102 (58.29)
Other	9 (5.14)
Ethnicity	
Hispanic	11 (6.29)
Non-Hispanic	164 (93.71)
GCS	
Eye score	4 (1–4)
Verbal score	4 (1–5)
Motor score	6 (4–6)
GCS total	13 (6–15)
GCS-P	12 (6–15)
GCS-NPi	12 (6–14.5)
avgNPi	3.73±1.31
Pupillary reactivity	
Both reactive	158 (90.29)
One reactive	3 (1.71)
Neither one reactive	14 (8.00)
NPi-right	3.72±0.11
NPi-left	3.74±0.11
Pre-morbid mRS	0
mRS at discharge	4 (2–5)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
GCS, Glasgow Coma Scale; GCS-P, GCS plus manual pupillary light reflex; GCS-NPi, GCS plus Neurological Pupil index; avgNPi, average NPi; mRS, modified Rankin Scale.

Table 2. Parameter estimates for total GCS, GCS-P, GCS-NPi, and avgNPi from non-linear mixed procedure

Parameter	Maximum likelihood estimate	Standard error	95% CI	*P*-value
Total GCS	−0.169	0.025	−0.218 to −0.120	<0.001
Sex[a]	−0.045	0.238	−0.514 to 0.424	0.850
Age	0.020	0.005	0.010 to 0.030	0.001
Ethnicity[b]	0.243	0.454	−0.653 to 1.138	0.594
GCS-P	−0.169	0.024	−0.216 to −0.122	<0.001
Sex[a]	−0.058	0.235	−0.522 to 0.406	0.806
Age	0.020	0.005	0.010 to 0.029	0.001
Ethnicity[b]	0.226	0.449	−0.660 to 1.112	0.615
GCS-NPi	−0.169	0.024	−0.215 to −0.122	<0.001
Sex[a]	−0.057	0.235	−0.520 to 0.407	0.809
Age	0.02	0.005	0.010 to 0.030	<0.001
Ethnicity[b]	0.231	0.449	−0.655 to 1.116	0.608
avgNPi	−0.394	0.090	−0.571 to −0.217	<0.001
Sex[a]	0.099	0.252	−0.398 to 0.596	0.695
Age	0.018	0.005	0.007 to 0.028	0.001
Ethnicity[b]	0.166	0.485	−0.790 to 1.123	0.732

GCS, Glasgow Coma Scale; GCS-P, GCS plus manual pupillary light reflex; GCS-NPi, GCS plus Neurological Pupil index; avgNPi, average NPi; CI, confidence interval.
[a]Male vs. female; [b]Hispanic vs. non-Hispanic.

$P < 0.001$), and for avgNPi was −0.39 (−0.57 to −0.22, $P < 0.001$). If the total GCS changes by 1 unit then the mRS score at discharge will change by −0.17. If the GCS-P changes by 1 unit, the mRS score at discharge will change by −0.17. If the GCS-NPi changes by 1 unit, the mRS score at discharge will change by −0.17. A 1-unit change in avgNPi will result in a change in the discharge mRS score by −0.39. Thus, increasing the GCS, GCS-P, GCS-NPi, and avgNPi scores will significantly decrease the mRS score ($P < 0.001$). Therefore, based on the four fitted models for each of the predictors (GCS, GCS-P, GCS-NPi, and avgNPi), all four predictors were good in predicting discharge mRS, with very similar MLEs. Age was also a significant independent predictor of mRS at discharge ($P < 0.001$) whereas, sex and ethnicity were not predictors of mRS at discharge ($P > 0.05$).

Table 3 shows results from the analysis of the absolute correlation between these four independent variables. These results revealed a strong significant correlation ($P < 0.05$) between these four predicting variables suggesting that any of these predictor variables can be used to predict mRS at discharge. The weakest correlation was seen between GCS-P and total GCS (correlation, 19%) while the strongest correlation was observed between avgNPi and total GCS (correlation, 94%). Furthermore, the correlations between GCS-NPi and total GCS (correlation, 78%), and GCS-P and GCS-NPi (correlation, 76%) were moderately strong.

Table 3. Correlation matrix of parameter estimates for the predicting variable

Parameter	Total GCS	GCS-P	GCS-NPi	avgNPi
Total GCS	1.000			
GCS-NPi	0.776		1.000	
GCS-P	0.185	1.000	0.763	
avgNPi	0.940	0.260	0.788	1.000

GCS, Glasgow Coma Scale; GCS-NPi, GCS plus Neurological Pupil index; GCS-P, GCS plus manual pupillary light reflex; avgNPi, average NPi.

DISCUSSION

This study compared the ability of GCS, GCS-P, GCS-NPi, and avgNPi to predict mRS outcome at discharge in a patient with TBI. Our findings show no statistical difference between the four variables and all of the variables were good predictors of mRS outcome at discharge in patients with TBI ($P < 0.001$). Although the pupilometer is more reliable and accurate than the manual pupillary evaluation (performed using a penlight), combining NPi with GCS did not predict mRS outcome at discharge better than using GCS alone, GCS-P, nor avgNPi for predicting outcome. Therefore, any of these predictor variables may be used to predict mRS outcome, due to the high correlation between them ($P < 0.05$). However, the correlations (weak to moderately strong) between total GCS, GCS-P, GCS-NPi, and avgNPi indicate that it would not be appropriate to use any pair of these variables to predict mRS at discharge because they are highly related and will result in

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multi-collinearity.

The present study is the first to examine the difference between the four predictor variables in predicting mRS outcome at discharge in patients with TBI. Previous studies have compared GCS alone with GCS-P, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II, Full Outline of UnResponsiveness (FOUR) score, and Kampala Trauma score in predicting the mortality among patients in neurocritical care or general critical care [30-32]. In a study by Brennan et al. [17] that compared GCS alone with GCS-P in predicting mortality, it was found that GCS-P was significantly better than GCS in predicting mortality as increasing the GCS-P was associated with a decrease in mortality which is similar to the results of our study that also indicate that a 1 unit change in GCS-P is associated with a –0.17 units change in mortality. Of note, in our study, GCS-P was derived was using AIP, an objective measure of PLR, given that AIP is more reliable than subjective assessment [19,22]. GCS-P in our sample is likely more representative of true GCS-P than previously reported.

A similar study in the past compared the FOUR score and GCS and also compared their inter-rater reliability but found no statistical difference ($P > 0.05$) between the two scores in predicting 28-day mortality among patients in general critical care however, the interrater reliability of the FOUR score was better than the GCS [31]. The FOUR score was developed with one of the assessments being pupillary examination [31]. Another study conducted in the past studied the predictive power of SAPS II, APACHE II, and GCS found no significant difference between the four variables in predicting mortality in neurosurgical patients, which isn't entirely similar to our study, but the results from our study also indicated no difference between the four variables in predicting mRS outcome in patients, with TBI [30].

As no significant difference is seen between the predictive ability of the four variables, using any of these tools to predict the functional outcome in patients at discharge after TBI will be equally useful. While there was no significant difference between GCS and the other predictor variables, using NPi alone has the advantage of being an objective measure and may be clinically more relevant than using GCS alone. Further, to be accurate, the GCS must be performed in the absence of a sedative or hypnotic effect [33]. Patients with TBI may have pharmaceutical effects as a result of treatment (e.g., the need for sedation to facilitate care), and this may impair the ability to perform an accurate GCS [34]. Although ocular instillation of medications is known to affect the PLR [35], the currently available evidence supports that the most common sedatives used in TBI care do not impair the PLR [21].

We believe that NPi, alone or combined with GCS may be clinically more reliable and useful than GCS alone due to the high interrater reliability of the pupilometer that measures the NPi in a few seconds [18,19]. However, small sample size is one of the limitations of our study. Although our sample was drawn from four U.S. hospitals and one hospital from Japan, and this increases the generalizability of the study. Our data is also limited in that we did not have TBI subtypes identified (e.g., open, closed, concussive, epidural, subdural, etc.). A recent study found that abnormal NPi was a strong predictor of the need for neurosurgical intervention after severe closed TBI [36]. There is still a need for a more reliable and objective tool for predicting functional outcomes in patients with TBI. Although the combination of GCS and NPi may be clinically more reliable and useful, it is not yet integrated into practice. Therefore, the addition of NPi to other prognostic models such as IMPACT and CRASH prognostic calculators that are easily available and accessible to all clinicians may be tested in prospective research studies to quantify prognosis in patients with TBI and for supporting clinical research and practice. We believe that future studies including a large sample size are required to study the differences in the predictive ability of the GCS-NPi in comparison to GCS, GCS-P, and avgNPi as well as to study the additional role of NPi to the prognostic models approach for predicting the mRS outcome in patients with TBI should be tested.

Our study concludes that any of the four predictors (GCS, GCS-P, GCS-NPi, and avgNPi) could be used as potential predictors in predicting mRS outcome at discharge among the study population. These findings suggest that the combination of PLR and GCS is not superior to NPi alone in predicting discharge mRS. Additional studies including a large study population is required to determine whether the combination of GCS and measures of the PLR improve prognostication.

ARTICLE INFORMATION

Ethics statement

The Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (ENDPANIC) registry is approved by the Institutional Review Board of the University of Texas Southwestern Medical Center (IRB No. STU_2015) and is granted waiver of consent.

Conflict of interest

No potential conflict of interest relevant to this article.

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