OBSERVATIONAL STUDY

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Early Pupil Abnormality Frequency Predicts Poor Outcomes and Enhances International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) Model Prognostication in Traumatic Brain Injury

Divya Veerapaneni, MD[1]
Naveen Arunachalam Sakthiyendran, BS[2]
Yili Du, MS[3,4]
Leigh Ann Mallinger, BS[3]
Allyson Reinert, BS[3]
So Yeon Kim, MPH[2]
Chuong Nguyen, BS[3]
Ali Daneshmand, MD, MPH[2,3]
Mohamad Abdalkader, MD[5]
Shariq Mohammed, PhD[4]
Josée Dupuis, PhD[4,6]
Kevin N. Sheth, MD[7]
Emily J. Gilmore, MD[8]
David Greer, MD, MA[2,3]
Charlene J. Ong, MD, MPHS[2,3]

IMPORTANCE: In patients with traumatic brain injury (TBI), baseline pupillary assessment is routine; however, the occurrence rate and clinical significance of pupil abnormalities over the early course of hospitalization remain poorly characterized.

OBJECTIVES: To determine whether the occurrence and frequency of pupil abnormalities within the first 72 hours of ICU admission are associated with unfavorable discharge outcomes and to assess whether incorporating this frequency improves the performance of an established prognostic model.

DESIGN, SETTING, AND PARTICIPANTS: This was a retrospective observational study of adults admitted with a primary diagnosis of TBI to a single tertiary care ICU between 2018 and 2022. Inclusion criteria included at least three quantitative pupillometry assessments within the first 72 hours.

MAIN OUTCOMES AND MEASURES: Quantitative pupillometry was used to calculate the Neurological Pupil index (NPi) at each assessment. Abnormalities were defined as NPi less than 3 in either eye, NPi asymmetry greater than or equal to 0.7, or pupil size asymmetry greater than or equal to 1 mm. The primary outcome was unfavorable discharge disposition (death, hospice, or long-term care). Multivariable logistic regression was used to evaluate the association between pupil abnormality frequency and outcomes, and model performance was compared using goodness-of-fit tests with and without pupil frequency added to the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) model.

RESULTS: Among 131 patients (median age, 59 yr; 30% women), 35% had an unfavorable discharge disposition. Pupil abnormalities occurred in 60% of mild, 61% of moderate, and 88% of severe TBI patients. For each 1% increase in the frequency of pupil abnormalities over 72 hours, the odds of unfavorable discharge increased by 3% (odds ratio, 1.03; 95% CI, 1.01–1.05). Adding pupil abnormality frequency to the IMPACT model improved its goodness-of-fit ($\chi^2 = 5.24$; $p = 0.02$).

CONCLUSIONS AND RELEVANCE: Pupil abnormalities are common across TBI severities, particularly in severe cases. A higher frequency of abnormal pupil measurements within the first 72 hours is associated with unfavorable outcomes and significantly enhances the predictive performance of established TBI prognostic models. Serial quantitative pupillometry may offer clinically valuable, dynamic prognostic information in the acute care setting.

KEYWORDS: abnormal pupil function; discharge disposition; prognostication; pupil anomalies; traumatic brain injury

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KEY POINTS

Question: What is the association between pupil abnormality frequency over the first 72 hours of admission and unfavorable discharge disposition, and does this improve the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) traumatic brain injury (TBI) model?

Findings: In this retrospective observational study of 131 TBI patients at a single center, we found that an increased frequency of pupil abnormalities across 72 hours was significantly associated with unfavorable discharge in patients and improved the IMPACT model's goodness-of-fit.

Meaning: These findings highlight the potential of long-term pupillary metrics as both a prognostic indicator for patients and a tool for enhancing the predictive accuracy of prognostic TBI models.

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide (1). Absent unilateral or bilateral pupil reactivity at admission is associated with worse outcomes in TBI patients (2, 3) and is used in the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) TBI model (4, 5), a well-established score for predicting clinical outcomes in patients with moderate and severe TBI. While manual pupillary assessment has historically been a core component of TBI assessment and management, its clinical relevance is most apparent when pupils are grossly unreactive. However, manual assessment is prone to variability and error. A study by Olson et al (6) demonstrated that interrater reliability between clinicians' assessment of nonreactive pupils was less than 50%. Quantitative pupillometry addresses these limitations by providing objective, reproducible measurements of pupil size and reactivity (7), enabling longitudinal assessment of subclinical decreased pupil reactivity. Previously, the lack of reliable quantitative thresholds hindered the ability to clarify the burden of poorly reactive pupils and their association with outcome.

Close neurologic monitoring, including subjective assessments of pupil size and reactivity, plays a key role in guiding clinical decision-making for TBI patients during hospitalization (8, 9). Furthermore, pupillometry has been shown to predict not only long-term outcomes (10) but also important in-hospital clinical events, including neurologic deterioration in patients with large ischemic stroke (11). To determine whether pupillometry in TBI could improve prognostication of deterioration, foundational study on occurrence rate and prevalence is necessary. Understanding the expected frequency of pupil abnormalities and their association with clinical outcomes in the first 72 hours post-TBI may improve detection of early neurologic deterioration and outcome prognostication.

Our aim was to determine the prognostic value of pupil abnormality frequency by: 1) characterizing the prevalence of pupil abnormalities within different TBI severities; 2) testing its association with clinical outcomes; and 3) investigating whether pupil abnormality frequency improves existing TBI prognostic models. We hypothesized that increased pupil abnormality frequency is associated with worse outcomes and that the inclusion of pupil abnormality frequency over the first 72 hours of admission improves TBI prognostication.

METHODS

Study Population

We conducted a single-center retrospective study of TBI patients admitted to the Boston Medical Center surgical and neurologic ICUs between 2018 and 2022 and who had at least three quantitative pupil measurements collected within the first 72 hours of hospitalization. Patients were identified through a screening of our preexisting pupillometry registry (Institutional Review Board [IRB] No: H-37699, October 9, 2018, Boston Medial Center IRB, Title: Quantitative Pupillometry in Patients With Critical Neurologic Injury [QUIP]). Exclusion criteria included preexisting eye conditions that may impact pupil reactivity, such as diabetic retinopathy and glaucoma (**eFig. 1**, https://links.lww.com/CCX/B502).

Data Collection

We collected demographic and clinical information from the electronic health record through the Clinical Data Warehouse (**eMethods**, https://links.lww.com/CCX/B502). Using the admission Glasgow Coma Scale (GCS) in the ICU post-resuscitation, patients were categorized as mild (GCS 13–15), moderate (GCS

9–12), or severe (GCS < 9) TBI (12). For each patient, we measured radiographic features, including midline shift and effacement of basal cisterns, from the most severe brain CT in the first 72 hours to compute the Marshall CT score (13), a radiographic classification system for TBI, after establishing interrater reliability of at least 0.70 (95% CI, 0.42–0.99). The most severe brain CT in the first 72 hours was used for the analysis to reflect the overall severity of the patient's condition after potential deterioration rather than the patient's baseline at admission.

Trained nursing staff collected pupillometry data using the NeurOptics NPI-300 pupillometer (NeurOptics, Irvine, CA) during standard neurologic checks (every 1, 2, or 4 hr). All patients receive pupillometry in the ICU unless contraindicated for severe facial trauma, consistent declining of pupillometry, or eye enucleation. The pupillometer reports the Neurological Pupil index (NPi), a composite score of pupil reactivity based on resting and constricted pupil size, percent change, constriction velocity, dilation velocity, and latency. NPi scores range from 0 to 5, with values less than 3 considered abnormal by the manufacturer. This report was prepared according to Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (14).

Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. Our patient population was gathered through an IRB approved chart review study with waived informed consent. This study qualifies for a waiver of informed consent because it presents no greater than minimal risk, involves no research intervention, and collects only standard-of-care data, with the only risk being related to data security, which will be mitigated by de-identification and destruction of the linking key after data analysis.

Outcomes

The primary outcome was unfavorable discharge disposition, defined as death, hospice, or long-term facility placement. Other outcomes included death at discharge, and documented evidence of eye tracking at discharge (eMethods, https://links.lww.com/CCX/B502). Outcomes were determined from discharge summaries and ascertained by two reviewers (D.V., C.J.O.).

Exposures

The primary exposure was pupil abnormality frequency calculated per patient and defined as the percentage of abnormal pupil measurements over 72 hours. Repeated pupil measurements within 1 hour were consolidated by using the minimum NPi, maximum Diff NPi, and maximum Diff Size to capture the most abnormal status in each 1-hour interval. Pupils were considered "abnormal" if NPi less than 3 in either eye, NPi asymmetry between eyes (Diff NPi) greater than or equal to 0.7, or size asymmetry between eyes (Diff Size) greater than or equal to 1 mm. Definitions were based on manufacturer recommendations (NPi < 3 and Diff NPi ≥ 0.7) (15). Other metrics, including constriction velocity, dilation velocity, and latency, are encompassed in the NPi variable. Secondary exposures were frequencies of unilateral and bilateral pupil abnormalities. Unilateral pupil abnormalities were defined as unilateral NPi less than 3, Diff NPi greater than or equal to 0.7, or Diff Size greater than or equal to 1 mm, whereas bilateral pupil abnormalities were defined as bilateral NPi less than 3. Diff Size and Diff NPi were considered unilateral pupil abnormalities since one abnormal pupil would be sufficient to make pupils asymmetric between eyes.

We also explored occurrence rate, which was defined dichotomously as present or absent if a pupil abnormality ever occurred during the first 72 hours in a patient. Sensitivity analyses, including only NPi less than 3, Diff NPi greater than or equal to 0.7 or size greater than or equal to 1 mm, were also performed (eMethods, https://links.lww.com/CCX/B502).

Analysis

Baseline cohort characteristics and pupil abnormality metrics were summarized for the full cohort and stratified by TBI severity group with categorical variables reported as frequency (proportion) and continuous variables reported as median (25th–75th percentiles). To compare differences among TBI severity groups, we used the chi-square test and Fisher exact test for categorical variables. For continuous variables, we employed analysis of variance and the Kruskal-Wallis test (eMethods, https://links.lww.com/CCX/B502).

To test our primary hypothesis, we performed multivariable logistic regression of pupil abnormality frequency and unfavorable discharge disposition after

adjusting for hypothesized confounders, including age, race, mechanism of injury, TBI severity, and Marshall CT score (16). We performed similar analyses using secondary exposures and outcomes and performed subgroup analysis of patients with moderate and severe TBI. We explored the model with additional potential clinical confounders, including whether the patient underwent interventions, including osmotic therapy or surgical decompression (craniectomy or craniotomy), and whether they experienced hypotension, hypoxemia, or extracranial injury (17). Given that the data were not normally distributed, reporting between the median or mean was chosen based on sample size and distribution.

To determine the prognostic value of pupil abnormality frequency, we modeled unfavorable discharge disposition and death at discharge in moderate and severe TBI using the core IMPACT TBI model and IMPACT plus pupil abnormality frequency over the first 72 hours. Features of the base IMPACT model included age, the motor component of GCS at admission, and pupil reactivity at admission. Pupil reactivity was defined subjectively and dichotomously as either bilateral or unilateral pupil reactivity, with bilateral pupil reactivity as the reference. We compared model goodness-of-fit using the likelihood ratio test and evaluated model performance using receiver operating characteristic (ROC) curve (eMethods, https://links.lww.com/CCX/B502) (18).

Significance threshold of α equals to 0.05 was used as our primary hypothesis. All other tests were hypothesis-generating only. Preprocessing and analysis of data were done using code publicly available at: https://github.com/fordivyav/TBI_Pupillometry (eMethods, https://links.lww.com/CCX/B502). The study was approved by the Boston Medical Center IRB. Informed consent was waived because of the anonymous nature of the study. Anonymized data for this study are available from the senior author (C.J.O.) upon reasonable request.

RESULTS

Cohort Characteristics

Our final cohort consisted of 131 patients with 3877 total pupil measurements. Thirty percent of the cohort was female. Median age was 59 years (38–72 yr; 25th –75th percentiles). Thirty-seven percent of patients (n = 48) had mild TBI, 14% (n = 18) had moderate TBI, and 50% (n = 65) had severe TBI. Seven percent (n = 9) of the cohort had penetrating injuries. Median Marshall CT score was 2 (2–5). Unfavorable discharge disposition occurred in 35% of patients (n = 46), with 22% of patients (n = 29) deceased upon discharge, with 4.6% of the total cohort who died before 72 hours (**eTable 1**, https://links.lww.com/CCX/B502).

Patients underwent a median of 21 (11–36) pupil measurements. Median time to first pupil measurement was 3 hours (2–6 hr). Median NPi over 72 hours was 4.4 hours (4.0–4.6 hr) (eTable 1, https://links.lww.com/CCX/B502). Seventy-four percent of TBI patients (n = 97) experienced at least one pupil abnormality. Of patients with at least one abnormal pupil measurement, 96% of patients (n = 93) experienced unilateral pupil abnormalities, and 26% (n = 25) experienced bilateral pupil abnormalities.

Median frequency of unilateral and bilateral pupil abnormalities was 9% (0–25%) and 0% (0–0%), respectively (**Table 1**; **Fig. 1**; and **eTable 2**, https://links.lww.com/CCX/B502). Patients with unfavorable discharge disposition had increased median frequency of pupil abnormalities compared with patients with favorable discharge disposition (26% [8–70%] vs. 8% [0–20%]) (**eFigs. 2** and **3**, https://links.lww.com/CCX/B502). In 28 patients (21%) who underwent surgical decompression, pupil size difference was significantly different from those without surgery (0.2 [0.2–0.3] vs. 0.3 [0.2–0.5]; p = 0.03; and **eTable 3**, https://links.lww.com/CCX/B502). No patients returned for secondary decompression.

Pupil Abnormalities Across TBI Severity Groups

There were significant differences observed in age, intracranial pressure (ICP) monitor use, and discharge outcomes among TBI severity groups (eTable 1, https://links.lww.com/CCX/B502). Patients with severe TBI were more likely to experience at least one pupil abnormality (88% severe vs. 60% mild vs. 61% moderate; p = 0.001) (Table 1). Bilateral pupil abnormality occurrence rate was much higher in severe TBI (32%) compared with mild and moderate TBI (6% each; $p < 0.001$) (Figs. 1 and **2**).The frequency of pupil abnormality differed across TBI severity groups as follows: 14% (7–50%) in severe, 6% (0–33%) in moderate, and 5% (0–20%) in mild (p = 0.001) (Table 1; and **eFig. 4**, https://links.lww.com/CCX/B502).

To gain insight into the relation between pupil abnormalities in patients without severe TBI, we

TABLE 1.
Occurrence Rate and Frequency of Pupil Abnormalities over first 72 hours in Traumatic Brain Injury Patients ($n = 131$)

Pupil Abnormality Data	Overall ($n = 131$)	Mild TBI ($n = 48$)	Moderate TBI ($n = 18$)	Severe TBI ($n = 65$)	p
Occurrence rate, *n* (%)					
Pupil abnormalities[a]	97 (74)	29 (60)	11 (61)	57 (88)	0.001
Unilateral pupil abnormalities[b]	93 (71)	28 (58)	11 (61)	54 (83)	0.01
Bilateral pupil abnormalities[c]	25 (19)	3 (6)	1 (6)	21 (32)	< 0.001
Frequency, median (Q1–Q3)[d]					
Pupil abnormalities[a]	11 (0–29)	5 (0–20)	6 (0–33)	14 (7–50)	0.001
Unilateral pupil abnormalities[b]	9 (0–25)	4 (0–20)	5 (0–33)	11 (4–25)	0.05
Bilateral pupil abnormalities[c]	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–5)	< 0.001

TBI = traumatic brain injury.
[a]Pupil abnormalities: Neurological Pupil index (NPi) < 3, NPi difference between both eyes (Diff NPi) ≥ 0.7, or size difference between both eyes (Diff Size) ≥ 1 mm.
[b]Unilateral pupil abnormalities: Unilateral NPi < 3, Diff NPi 0.7, or Diff Size ≥ 1 mm.
[c]Bilateral pupil abnormalities: Bilateral NPi < 3.
[d]Frequency: Percentage of observations that have specific pupil abnormalities over all observations consolidated in hourly increments in first 72 hr per patient.
Univariate analysis of occurrence rate and frequency characteristics over first 72 hr and TBI severity groups. Occurrence rate of all pupil abnormalities and frequency of pupil abnormalities and bilateral pupil abnormalities differed significantly among TBI severity groups.

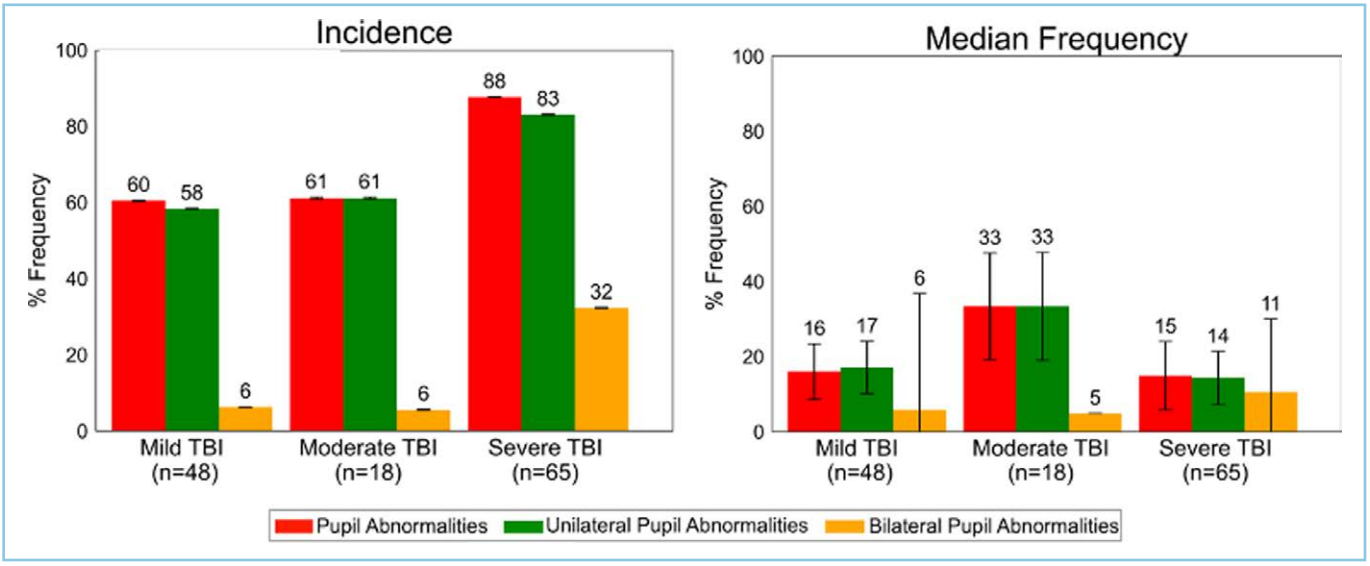

Figure 1. Percent occurrence rate and median frequency of pupil abnormalities between traumatic brain injury (TBI) severity groups ($n = 131$). Percent occurrence rate and median frequency of pupil abnormalities. Occurrence rate and median frequency of unilateral pupil abnormalities were higher compared with bilateral pupil abnormalities across most TBI severity groups. Frequency was reported as percentage of abnormal pupil measurements consolidated across hourly increments. Pupil abnormalities: Neurological Pupil index (NPi) less than 3, NPi difference between both eyes (Diff NPi) greater than or equal to 0.7 mm, or size difference between both eyes (Diff Size) greater than or equal to 1 mm. Unilateral pupil abnormalities: Unilateral NPi less than 3, Diff NPi greater than or equal to 0.7, or Diff Size greater than or equal to 1 mm. Bilateral pupil abnormalities: Bilateral NPi less than 3.

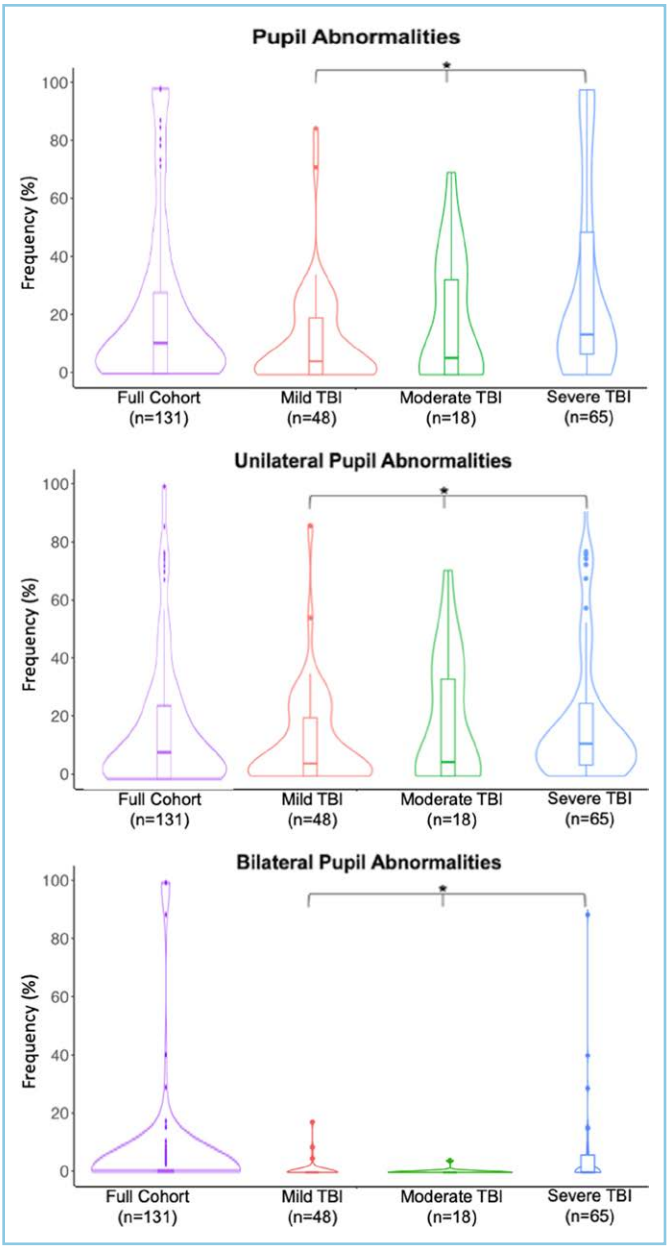

Figure 2. *Violin plots* of pupil abnormality frequency by traumatic brain injury (TBI) severity. Pupil abnormalities, including unilateral and bilateral pupil abnormalities, differed significantly across all TBI severity groups. Frequencies were reported as percentages of abnormal pupil measurements consolidated across hourly increments. Pupil abnormalities and unilateral pupil abnormalities occurred in all TBI severity groups, with increased median frequency associated with increased TBI severity. In contrast, bilateral pupil abnormalities were rare in the full cohort with most bilateral pupil abnormalities occurring in severe TBI. *Statistically significant difference across TBI severity groups ($p < 0.05$).

describe the hospital courses for mild and moderate TBI patients with NPi less than 3 (**eTable 4**, https://links.lww.com/CCX/B502).

Pupil Abnormality Frequency and Discharge Disposition

In our adjusted multivariable model, we found that a 1% increase in pupil abnormality frequency was associated with unfavorable discharge disposition (odds ratio [OR], 1.03; 95% Cl, 1.01–1.05). We observed that the OR increased in our stratified analysis of bilateral pupil abnormality frequency (OR, 1.21; 95% CI, 1.06–1.48) but not in unilateral pupil abnormality frequency (OR, 1.02; 95% CI, 1.00–1.04) (**Table 2**). Both bilateral and unilateral pupil abnormality frequency were associated with mortality (Table 2). Comprehensive results, including analysis of our moderate and severe TBI subgroup, and single pupil abnormality features are included in **eTables 5–8** (https://links.lww.com/CCX/B502). The significant association remained when we adjusted for additional clinical factors in the multivariable models (**eTable 9**, https://links.lww.com/CCX/B502).

IMPACT Score

The likelihood ratio test revealed that the IMPACT model plus pupil abnormality frequency had an improved goodness-of-fit compared with the core IMPACT model alone when predicting unfavorable discharge disposition ($\chi^2 = 5.24$; $p = 0.02$) (**Fig. 3**; and **eTable 10**, https://links.lww.com/CCX/B502). The IMPACT model for death at discharge also showed improved goodness-of-fit with the addition of pupil abnormality frequency ($\chi^2 = 14.95$; $p < 0.001$) (eTable 10, https://links.lww.com/CCX/B502). Absent bilateral pupil reactivity at baseline ($\beta = 14.74$) and pupil abnormality frequency ($\beta = 2.00$ per 1% increase) were the most important coefficients for predicting unfavorable discharge disposition and death at discharge (**eTable 11** and **eFig. 5**, https://links.lww.com/CCX/B502). The IMPACT model, including pupil abnormality frequency, had a nonstatistically significant improvement in discriminating the primary outcome compared with the core IMPACT model (area under the curve [AUC] 0.78 vs. 0.75; $p = 0.244$) (**eFig. 6**, https://links.lww.com/CCX/B502). However, AUC was significantly higher for predicting death at discharge (AUC 0.89 vs. 0.81; $p = 0.048$) (eFig. 6, https://links.lww.com/CCX/B502).

TABLE 2.
Multivariable Models of Pupil Abnormalities Frequency on Discharge Outcomes ($n = 131$)

	Unfavorable Discharge Disposition		Death at Discharge	
Frequency[a]	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Pupil abnormalities[b]	1.03 (1.01–1.05)	0.003	1.05 (1.03–1.07)	< 0.001
Unilateral pupil abnormalities[c]	1.02 (1–1.04)	0.136	1.02 (1–1.04)	0.04
Bilateral pupil abnormalities[d]	1.21 (1.06–1.48)	0.021	1.23 (1.08–1.51)	0.018

n = number of patients in full cohort with specified pupil abnormality, OR = odds ratio.
[a]Frequency: Calculated for every 1% increase in frequency.
[b]Pupil abnormalities: Neurologic Pupil index (NPi) < 3, NPi difference between both eyes (Diff NPi) ≥ 0.7, or size difference between both eyes (Diff Size) ≥ 1 mm.
[c]Unilateral pupil abnormalities: Unilateral NPi < 3, Diff NPi ≥ 0.7, or Diff Size ≥ 1 mm.
[d]Bilateral pupil abnormalities: Bilateral NPi < 3.
Multivariable logistic regression models were adjusted for age, race, severity group of traumatic brain injury, Marshall CT score, and penetrating vs. blunt trauma. Frequency was reported as percentage. Frequency of pupil abnormalities and bilateral pupil abnormalities were associated with unfavorable discharge disposition and death at discharge. All pupil abnormalities were associated with death.

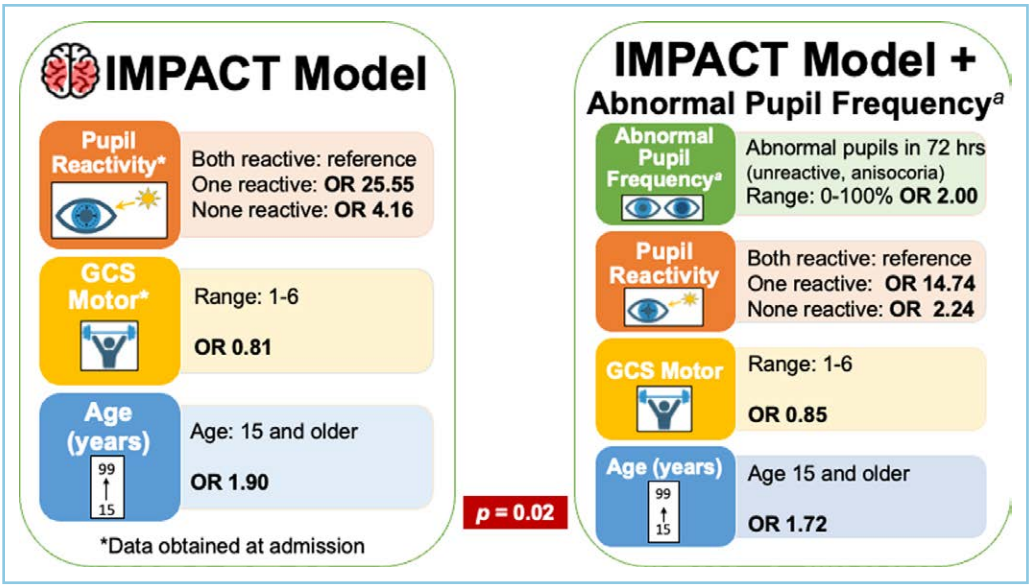

Figure 3. Schematic for International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury (IMPACT) model with and without abnormal pupil frequency. Created with BioRender.com. The IMPACT model consisted of pupil reactivity at admission (both, one, or neither reactive), Glasgow Coma Scale (GCS) motor component at admission, and age trained on our study cohort. The IMPACT model with pupil abnormality frequency over the first 72 hr of admission with data consolidated across hourly time intervals had improved goodness-of-fit ($p = 0.02$) compared with the IMPACT model alone. [a]Abnormal pupil frequency: Pupil abnormality frequency over the first 72 hr of admission (Neurological Pupil index [NPi] < 3, NPi difference between both eyes ≥ 0.7, or size difference between both eyes ≥ 1 mm). OR = odds ratio.

DISCUSSION

In this study, we found that increased frequency of abnormal pupil measurements within the first 72 hours of admission is associated with unfavorable discharge outcomes and improves goodness-of-fit of the IMPACT TBI model, which relies on a subjective pupil reactivity assessment at baseline. These findings are significant because longitudinal pupillometric data are not routinely used for prognostication or treatment decisions but has the potential to improve care.

Our study reveals that abnormal pupil measurements over the first 72 hours are common among TBI patients admitted to the ICU (74%), especially in severe TBI (88%). While patients with severe TBI are more likely to experience at least one pupil abnormality, they remain common among moderate and mild TBI patients as well. Our observation that at least one NPi less than 3 occurred in 42% of patients is consistent with results from a recent prospective study investigating the association of abnormal pupil

reactivity in patients with heterogeneous acute brain injury (40%) (11). The difference in prevalence of unilateral (71%) and bilateral (19%) pupil abnormalities in patients who had at least one abnormal pupil measurement is most likely because of the more inclusive definition we used for unilateral pupil abnormalities, including size difference and NPi difference.

In patients who experienced pupil abnormalities, the median frequency over the first 72 hours was higher in moderate and severe TBI patients compared with those with mild TBI. While moderate TBI patients had a nonstatistically significant higher frequency of pupil abnormalities than severe TBI patients, we posit this may be because they experienced neurologic worsening events within the first 72 hours of admission (eTable 4, https://links.lww.com/CCX/B502), evidenced by the significant association between increased pupil abnormality frequency and discharge disposition.

Our review of mild and moderate TBI patients with NPi less than 3 revealed that patients with mild TBI and pupil abnormalities were frequently complicated by intraparenchymal or subdural hemorrhages, some of which underwent surgical treatment (**eResult**, https://links.lww.com/CCX/B502). We infer that these cases support the hypothesis that pupil abnormality occurrence rate and frequency signify increased severity that may not be reflected at admission. This finding is likely reflective that patients with milder TBI phenotypes at admission can deteriorate during the hospital course. Following quantitative pupillometry in moderate or even mild TBI patients may be important to identify neurologic worsening, which can occur in 35% of TBI patients within the first 24 hours of admission (19).

Our findings regarding the association of pupil abnormality frequency and outcome are consistent with prior studies examining quantitative poor pupil reactivity over admission in heterogeneous causes of acute brain injury or in small case series of TBI (20–22). Our observation that the relation between pupil abnormality frequency and outcome remains significant for bilateral but not for unilateral pupil abnormalities may be because of the fact that the bilateral abnormalities can signify irreversible intrinsic damage to pathways for recovery in the midbrain and brain stem, whereas unilateral abnormalities may be more context-dependent and reversible. Our finding that the relationship between pupil abnormality frequency and outcomes remains significant for bilateral but not unilateral abnormalities may be because bilateral abnormalities indicate irreversible damage to midbrain and brainstem recovery pathways, whereas unilateral abnormalities may be more context-dependent and potentially reversible.

Our study demonstrates that the inclusion of pupil abnormality frequency over the first 72 hours of admission improves goodness-of-fit for current prognostic models. While there was an observed improvement in the ROC curves for the IMPACT TBI models with the addition of pupil abnormality frequency, the improvement was not statistically significant for the primary outcome. For the secondary outcome of death at discharge, the improvement of discriminatory was statistically significant. As this analysis was exploratory, results are hypothesis-generating. This suggests that while pupil abnormality frequency may offer incremental prognostic information, the findings should be interpreted cautiously, particularly given the study's limited sample size and statistical power for certain analyses.

Beyond its role in prognostication, quantitative pupillometry could potentially have utility in guiding acute management decisions. Frequent pupillometry could serve as one component of a noninvasive monitoring battery to detect early signs of neurologic deterioration, potentially prompting timely interventions, such as ICP management or escalation of care. While there is not a direct linear relation to elevated ICP in heterogeneous brain injury (11), we suspect that further understanding of how injury volume and location influence decreasing pupil reactivity is required and further study is needed.

This study has several limitations. As a retrospective observational study, it cannot establish causality or fully account for confounding factors, including pain, ambient light, or cognitive load—factors known to influence pupil reactivity (23–25). We also acknowledge that we did not have access to data on neurologic deterioration or post-discharge functional outcomes, which are necessary to elucidate the full prognostic utility of pupillometry.

Although we used discharge disposition as a surrogate measure, as in previous studies (26–29), we acknowledge its limitations. Moreover, we did not control for pain, ambient light, or cognitive load, which have been shown to affect pupil reactivity (23–25). Because we identified patients through an ongoing pupillometry registry, we cannot rule out selection bias. While our study was single center with a relatively small sample size, a post hoc analysis revealed

we had a power of 98% with a sample size of 131 when detecting the observed difference in abnormal pupil frequency between patients with favorable and unfavorable outcomes. Our aggregation of percentages of abnormal measurements across the first 72 hours may have obscured dynamic changes in pupil reactivity that could be clinically meaningful. Future studies examining temporal trends could provide valuable insights into early signs of neurologic worsening, potentially offering a more precise prediction of outcomes, and is the subject of an ongoing study.

Additional tests for other exposures were not powered sufficiently and thus are hypothesis-generating only. We had varying number of measurements per patient, which can lead to bias. Moreover, we acknowledge that early mortality or withdrawal of life-sustaining therapy (WLST) before 72 hours may have confounded results, though this was a minority of our patients (4.6%). The lack of standardization in WLST procedures, particularly beyond 72 hours, may have introduced variability affecting the consistency of our measurements. Future studies should aim to implement and adhere to standardized WLST protocols to ensure more uniform data collection and strengthen the reliability of pupillary metrics in prognostication. While we conducted multiple tests of association, we selected only one primary hypothesis to minimize this risk of false-positive associations. We acknowledge that the IMPACT model was designed to detect unfavorable outcome and 6-month mortality, and that we did not have access to long-term follow-up to compare outcomes as originally designed. Finally, it is important to note that while inclusion of pupil abnormality frequency had a statistically significant improvement in goodness-of-fit, it did not have a significant improvement in discrimination via AUC for our primary outcome and therefore should be interpreted cautiously. Further studies are needed to validate our findings.

Despite these limitations, our study has several strengths. We analyzed over 3000 unique pupil measurements from a diverse and heterogeneous patient cohort. Additionally, we conducted subgroup analyses and examined clinically meaningful outcomes to gain deeper insights into pupil abnormalities in TBI. Our study provides important foundational data that recognition and quantification of multiple abnormal pupil metrics (rather than simply nonreactive pupils) may enhance prognostication and possibly patient care.

CONCLUSIONS

Pupil abnormalities are common in TBI patients over the first 72 hours of injury, especially in those with severe TBI. Increased pupil abnormality frequency may be associated with higher risk of unfavorable discharge disposition, and pupil abnormality inclusion improves goodness-of-fit of the IMPACT TBI model for prognostication. Future studies should be conducted to further evaluate and externally validate whether the inclusion of pupil abnormality frequency in current models improves prognostication and treatment decisions.

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1 *Department of Neurology, The University of Texas Southwestern Medical Center, Dallas, TX.*

2 *Boston University Chobanian and Avedisian School of Medicine, Boston, MA.*

3 *Department of Neurology, Boston Medical Center, 1 Boston Medical Center Pl, Boston, MA.*

4 *Department of Biostatistics, Boston University School of Public Health, Boston, MA.*

5 *Department of Radiology, Boston Medical Center, 1 Boston Medical Center Pl, Boston, MA.*

6 *Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada.*

7 *Center for Brain and Mind Health, Yale School of Medicine, New Haven, CT.*

8 *Department of Neurology, Yale School of Medicine, New Haven, CT.*

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Drs. Ong and Veerapanemi were involved in designing the study. Ms. Yeon Kim was involved in data acquisition. Dr. Veerapaneni, Dr. Ong, and Mr. Arunachalam Sakthiyendran were involved in data analysis and interpretation. Dr. Veerapaneni, Dr. Dupuis, Dr. Ong, and Mr. Arunachalam Sakthiyendran were involved in drafting the original article. Dr. Veerpaneni, Dr. Daneshmand, Dr. Sheth, Dr. Abdalkader, Dr. Greer, Dr. Mohammed, Dr. Gilomre, Dr. Dupuis, Dr. Ong, Mr. Arunachalam Sakthiyendran, Ms. Mallinger, Ms. Reinert, and Ms. Du were involved in critical revisions. Drs.

Daneshmand and Abdalkader were involved in validation. Dr. Veerapaneni and Mr. Nguyen were involved in helping with data analysis software. Ms. Yeon Kim was involved in helping with project administrative tasks and resources. Dr. Ong was involved in supervising and acquiring funding for the project.

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Dr. Veerapaneni and Mr. Arunachalam Sakthiyendran contributed equally to this work.

For information regarding this article, E-mail: cjong@bu.edu

This study is adherent to ethical guidelines and approved by the Boston Medical Center Institutional Review Board.

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