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REVIEW ARTICLE

A Systematic Review Assessing the Current State of Automated Pupillometry in the NeuroICU

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Abstract

The aim of this study was to assess the current state of automated pupillometry technology and its application in the neurointensive care unit (neuroICU). We performed a literature search using the PubMed, MEDLINE, and EMBASE databases from database inception through a search end date of October 18, 2018, to identify studies reporting on the use of automated pupillometry in the care of critically ill patients with neurological impairment. Two independent reviewers reviewed all titles and abstracts in two filtering phases. Data were extracted independently. One hundred and forty-one articles/abstracts have been published on the use of automated pupillometry in critical care since inception of the PubMed, MEDLINE, and EMBASE databases. We selected and reviewed 22 full-text articles and 8 abstracts, of which 26 were prospective, 2 were retrospective, and 2 were larger case series. Automated pupillometry increased precision, reliability, and reproducibility compared with the manual pupillary examination; detected subtle and early pupillary changes; detected pupillary changes that indicate a rise, or impending rise, in intracranial pressure detected level of analgesia and depth of sedation; served as a prognostic indicator; estimated the clinical severity of aneurysmal subarachnoid hemorrhage; and served as a noninvasive monitor of response to osmotic therapy. At present, no consensus guidelines exist endorsing routine use of automated pupillometry in the neuroICU. However, an increasing quantity of research supports the usefulness of automated pupillometry in this setting. Further large-scale prospective studies are needed before updated consensus guidelines recommending widespread adoption of automated pupillometry are produced.

Keywords: Neurological examination, Reflex, Pupillary, Diagnosis, Computer-assisted, Diagnostic techniques, Ophthalmological, Monitoring, Physiologic

Introduction

Close monitoring of neurological status is employed in multiple clinical settings, as many conditions predispose to neurological deterioration related to cerebral edema and increasing intracranial pressure (ICP). These include, but are not limited to, postoperative neurosurgery, hypothermia after cardiac arrest (CA), acute ischemic or hemorrhagic stroke, brain tumors, and head injury [1]. Traumatic brain injury (TBI) alone affects more than 2.8 million Americans annually [2].

Neuromonitoring is essential to the detection of abnormalities in cerebral perfusion, oxygenation, chemistry, and function to support measures for regeneration from primary brain damage and to prevent secondary brain damage [3]. Additionally, intense clinical monitoring is an integral part of the management of patients at risk of neurological deterioration because neurological worsening may occur rapidly and signs and symptoms may be subtle [4, 5]. Neurological deterioration is associated with poor outcomes; therefore, at-risk patients are routinely monitored every 30–60 min, or more frequently.

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These serial neurological examinations provide important information that guides clinical decision making [4]. Thus, nursing and medical staff who regularly attend to these patients must be adept at performing thorough neurological assessments [5].

Neurointensive care units (neuroICUs) apply various methods for monitoring neurological function, as patients are often unable to participate in clinical examinations due to their critical condition and/or sedation [3]. The adoption of new technologies to assist clinical staff in their serial assessments of neurological status has been common practice in neuroICUs [3]. In 2014, a Neurocritical Care Society (NCS) expert group, in collaboration with the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the Latin American Brain Injury Consortium, assessed widely used methods for neuromonitoring and published consensus summary recommendations to guide healthcare professionals who routinely apply these technologies. Invasive methods for neuromonitoring, such as by probes and catheters, were prioritized in severe brain injury and thought to be fairly accurate, reliable, and valid [6–8]. However, the disadvantages of invasive methods are noted to be numerous. Invasive methods are expensive, cannot easily be changed or readapted, may require neurosurgical assistance, often require imaging to control the probe location, and, importantly, carry a risk of bleeding and infection [3]. A recent descriptive review of commonly applied noninvasive neuromonitoring methods, including transcranial ultrasound, evoked potentials, electroencephalography, near-infrared spectroscopy, and the emerging noninvasive technologies of bispectral index, bioimpedance, cranial accelerometry, and pupillometry concluded that, in addition to their noninvasive nature, these methods provide important advantages of repeatability, adjustability, low cost, and easy execution and interpretation [3].

Pupillometry is an emerging technology of particular interest because the pupillary examination is established as a fundamental element of any neurological assessment [9]. Abnormalities of pupillary response are associated with neurological deterioration and correlated with poor neurological outcomes [10]. In the clinical setting, pupil size, shape, symmetry, and the pupillary light reflex are most commonly tested manually by clinicians and nurses [11, 12]. However, there are intra- and interobserver disparities in interpreting the results, especially in the extremities of pupil size [12–14]. This has led to the development of automated objective pupillometers. The pupillometer is a handheld, portable, user-friendly, automated, accessible, inexpensive device with the capability to perform reproducible, precise, and quantitative measurements [14]. Although there are variations in the make of automated pupillometers available on the market, the working principle is the same and most devices assess similar parameters. Common parameters evaluated include the pupillary light reflex, pupil diameter and shape, onset latency, constriction and dilatation velocities, and percentage/ratio reduction in amplitude [3].

The 2014 NCS consensus conference did not recommend the use of automated pupillometry for routine neuromonitoring and instead stressed that automated pupillometry needs more development and validation through randomized controlled trials and careful observational studies [6]. However, various studies published both prior to and since 2014 demonstrate automated pupillometry's value in the clinical setting. Since the conference, hospitals have quickly adopted a practice that includes automated pupillometry technology, with neurocritical care at the forefront of this trend [12, 15, 16]. As of the last fiscal quarter, 295 hospitals in the USA have adopted the use of NeurOptics® pupillometers, one of the leading commercial brands. The company now has a presence in over 23 countries worldwide [17]. This has led to a corresponding increase in the quantity of research published on automated pupillometry and its usefulness as an assessment tool. However, despite the increase in available research and continued advancements in pupillometry technology, there have been no new consensus guidelines published as to the use of automated pupillometers in the neurointensive care setting.

With this systematic review, we aim to assess the specific outcomes associated with the use of automated quantitative pupillometry in neuromonitoring of critically ill patients with neurological impairment who receive care in a critical care setting. Additionally, we examine whether the specific outcomes associated with the use of automated quantitative pupillometers in this patient population have any effect on patient outcomes and assess potential limitations to wider adoption of automated pupillometry technology. We also consider whether there is now sufficient evidence to validate routine use of automated quantitative pupillometry in the care of these patients.

Methods

We performed a systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A literature search using the PubMed, MEDLINE, and EMBASE databases was performed from database inception through a search end date of October 18, 2018. Original studies with human subjects reporting on specific outcomes associated with the use of automated quantitative pupillometry to monitor critically ill patients with neurological impairment in a critical care setting were eligible for inclusion. Articles and abstracts published in English with study populations of 15 patients or more were included. Smaller case reports and case series were excluded. There was no limitation on type of publication.

We used the keyword "pupillometry" and at least one of the following terms or phrases in our search: neurocritical care, intracranial pathology, neurological monitoring, intracranial pressure, herniation, head trauma, intensive care, critical care, intracranial lesions, critically ill patients, outcomes, and prognosis. This primary database search provided 135 records after removal of duplicates. Six additional records were identified through text references and communication with researchers in the field, for a total of 141 titles/abstracts. Two independent reviewers (S.P. and C.M.) reviewed all titles and abstracts in the first of two filtering phases, providing 8 abstracts and 24 full-text manuscripts for further review and inclusion.

In the second filtering phase, the same reviewers evaluated full-text manuscripts for eligibility, providing 22 articles for inclusion, in addition to the 8 abstracts, for a total of 30 records. The first of two excluded full-text articles did not meet criteria for an original study and the second failed to control for intra- and inter-patient variability, rendering results inconclusive. All 30 records comprising original articles and abstracts were included and thoroughly reviewed by the same reviewers with no discrepancies. Data extraction was performed independently.

We determined the study quality for each study using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, with randomized trials given a high grade, observational studies a low grade, and any other evidence, a very low grade. Applying the patient–intervention–comparison–outcome (PICO) format to our data, the patient problem was the pupillary examination, the intervention was the automated quantitative pupillometer, and the comparison was the manual examination. Primary outcomes assessed included the ability of automated pupillometry to increase precision, reliability, and reproducibility compared with the manual pupillary examination; detect subtle and early pupillary changes; detect pupillary changes that indicate a rise, or impending rise, in intracranial pressure (ICP) detect level of analgesia and depth of sedation; serve as a prognostic indicator; estimate the clinical severity of aneurysmal subarachnoid hemorrhage (aSAH); and serve as a noninvasive monitor of response to osmotic therapy. Secondary outcomes assessed included the ability of automated quantitative pupillometry to affect clinical outcomes and whether sufficient evidence exists to validate routine use of automated quantitative pupillometry in the care of critically ill patients in the neuroICU. We also examined how cost, variety of pathology, environmental factors, and presence of medical comorbidities may influence the use of automated pupillometry and serve to limit wider adoption of the technology. Our systematic review includes relevant data from all 30 records and provides an updated assessment of the utility of automated pupillometry in the care of critically ill patients with neurological impairment based on the current literature.

Results

One hundred and forty-one articles and abstracts have been published on this subject since inception of the PubMed, MEDLINE, and EMBASE databases. After review, we selected 22 manuscripts and 8 abstracts that met eligibility criteria for inclusion according to the PRISMA Flow Diagram (Fig. 1). All 30 records were original studies with human subjects, of which 26 were prospective, 2 were retrospective, and 2 were larger case series. Table 1 summarizes the studies and main findings.

Increased Precision, Reliability, and Reproducibility

The increased precision, reliability, and reproducibility of automated pupillometry compared to manual examinations were evaluated by six studies included in this review [11, 14, 18–21]. In all cases, automated pupillometry was superior to manual pupillometry. Meeker et al. [11] found that the median absolute error in measuring pupil size using manual examination is over twice as large when compared to an automated pupillometer (0.54 mm, 95% CI 0.51–0.62 vs. 0.23 mm, 95% CI 0.20–0.31). Couret et al. [20] showed a 19% rate of discordance in pupil size measurements between manual examination by nurses and automated pupillometry for pupils between 2 and 4 mm in size. This discrepancy increased to 39% for pupils less than 2 mm. Additionally, trained neurocritical care nurses did not detect 50% of cases of anisocoria and wrongly detected 16 cases of anisocoria.

Olson et al. [14] measured inter-examiner reliability using Cohen's kappa coefficient (k) and showed that reliability between two independent practitioners performing manual pupillary assessments was only moderate for pupil size ($k = 0.54$, 95% CI 0.50–0.57) and only fair between the two independent practitioners and pupillometers ($k = 0.29$, 95% CI 0.27–0.32 and $k = 0.31$, 95% CI 0.28–0.34) for the first and second practitioners, respectively. Yan et al. [19] also found lower inter-examiner disagreement using the automated pupillometer compared to manual pupillometry when measuring pupil size in patients with absent pupil reactivity (4.5% vs. 27.3%, $p < 0.05$) and sluggish pupil reactivity (4.5% vs. 31.8%, $p < 0.05$).

Assessing inter-device reliability, Zhao et al. [21] determined that Cohen's kappa assessments (k) for pupil size

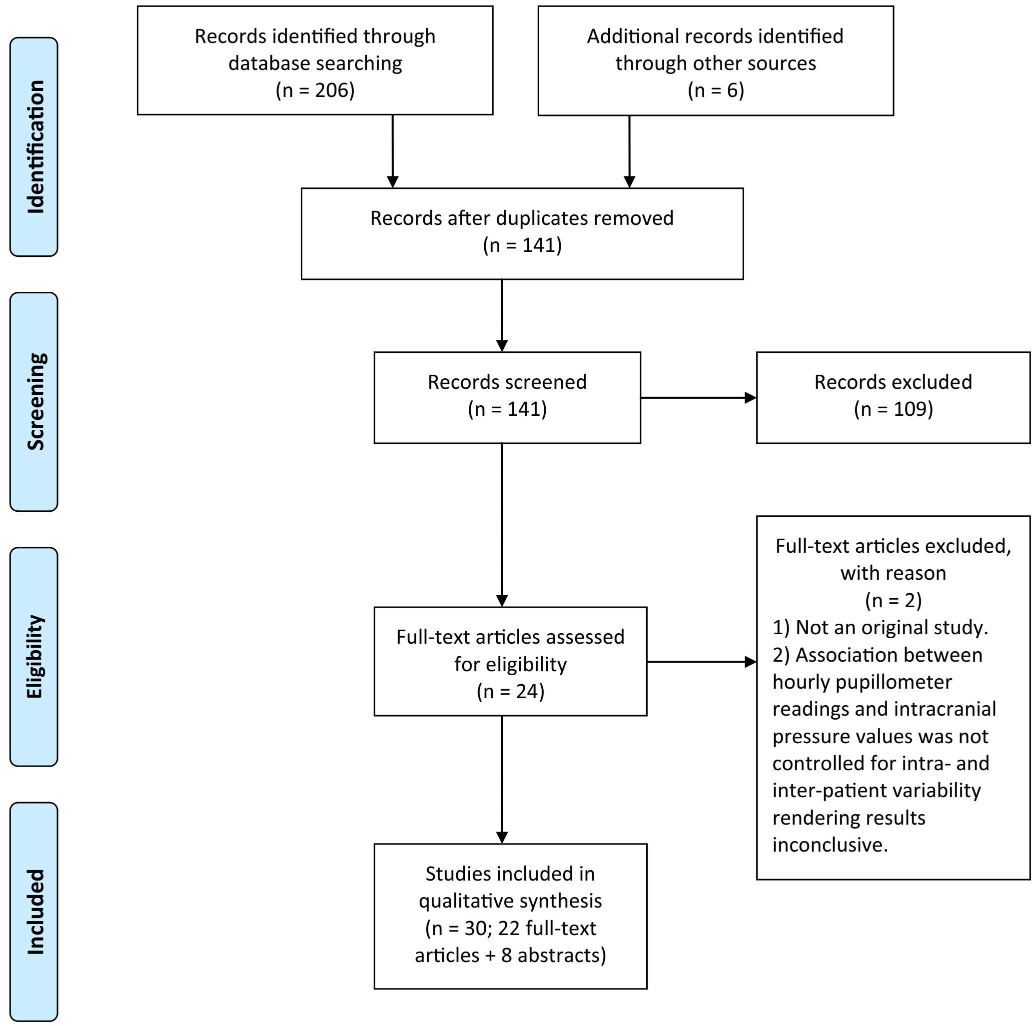

Fig. 1 PRISMA flow diagram. From: From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org

and reactivity showed almost perfect agreement between two identical NeurOptics® NPi™-100 pupillometers for maximum pupil size ($k=0.97$ left eye, $k=0.91$ right eye), minimum pupil size ($k=0.96$ left eye, $k=0.98$ right eye), and pupil reactivity ($k=0.99$ left eye, $k=0.90$ right eye).

Detection of Subtle Pupillary Changes

Several studies examined the ability of automated pupillometry to detect subtle pupillary changes and do so earlier than manual examination [14, 19, 22, 23]. Prior research has shown that routine manual evaluation with traditional penlight is unable to detect the presence of a pupillary light reflex (PLR) when the amplitude is < 0.3 mm [22]. Olson et al. [14] found that automated pupillometry could detect a light reflex in 66.7% of pupils that were scored as non-reactive by practitioners. Larson et al. [22] determined that 44% of comatose ICU patients assessed to have no PLR on manual examination were found to have a detectable PLR using automated pupillometry.

Additionally, Shoyombo et al. [23] found that automated pupillometers were better able to detect subtle and unexpected changes in the PLR by capturing many variables simultaneously and normalizing data using pupillary index technology, specifically the neurological pupil index (NPi) function of automated pupillometers manufactured by NeurOptics®. They found that when measuring NPi and constriction velocity (CV), two distinct variables for characterizing the PLR, an NPi of less than 3.0 (abnormal), did not automatically correspond to

Table 1 Summary of the literature

References	*n*	Description of study	Main findings	Limitations	GRADE
Tamura et al. [33]	50	Multicenter single-arm, uncontrolled, prospective, observational study Analysis of ability of quantitative automated pupillometry to predict the outcome of post-CA patients during first 72 h after the ROSC	PLR values were consistently higher in survivors compared to non-survivors at 90 days. PLR value was associated with 90-day survival ($p < 0.001$) PLR values were consistently higher in patients with a good neurological outcome (CPC 1–2) compared to those with poor neurological outcomes (CPC 3–5) at 90 days 0-h PLR value was the best predictor of 90-day survival (AUC value of 0.82 and PLR cutoff value of 3%) and good neurological outcome at 90 days (AUC value of 0.84 and PLR cutoff value of 6%) Concludes that quantitative measurement of PLR has prognostic value as early as within 1 h after return of spontaneous circulation	Small sample size Many patients excluded due to inability to obtain informed consent immediately after return of spontaneous circulation Does not compare prognostic accuracy of quantitative PLRs with physiologic or biomarker tests widely used in post-CA prognostication	Low
Solari et al. [34]	103	Prospective, blinded observational cohort Analysis of ability of quantitative automated pupillometry to predict neurological recovery after CA	Survivors had higher quantitative PLR (median 20% vs. 11%, $p < 0.0001$) expressed as % change of PLR and CV (1.46 mm/s vs. 0.94 mm/s, $p < 0.0001$) than non-survivors At 48 h, a quantitative PLR of < 13% had 100% specificity and positive predictive value to predict poor recovery (0% false-positive rate) and equaled the prognostic value of EEG and SSEP	Single-center design Study design evaluated automated pupillometry at 24 and 48 h, limiting extrapolation of data to later time points Quantitative PLR has lower accuracy to predict good recovery (sensitivity 61%, negative predictive value 71%)	Low
Suys et al. [35]	50	Prospective, observational, double-blinded study Examined accuracy of using automated infrared pupillometry to predict the outcome of post-CA coma, compared to the standard PLR, EEG, and SSEP	Patients with good outcomes (CPC 1–2) were more likely to have higher PLR at day 1 (16% vs. 10%, $p < 0.001$) and day 2 (20% vs. 11%, $p < 0.001$) than those with poor outcomes (CPC 3–5) The best cutoff for outcome prediction of quantitative PLR was < 13% AUC values for quantitative PLR to predict poor outcome was higher on day 1 (0.79 vs. 0.56, $p = 0.005$) and Day 2 (0.81 vs. 0.64, $p = 0.006$) than for standard PLR Comparison of AUC values for quantitative PLR versus EEG (0.81 vs. 0.80, $p > 0.20$) and quantitative PLR versus SSEP (0.81 vs. 0.73, $p > 0.20$) shows similar accuracy, but results are not significant Concludes that quantitative PLR, as measured by automated pupillometry, is more accurate than standard PLR in predicting outcome of post-anoxic coma, and is comparable to EEG and SSEP in prognostic accuracy. These findings were irrespective of hypothermic conditions and sedation	Small sample size, single-center Early stage of prognostic assessment (within 48 h of CA) All poor outcome patients died, unable to predict neurological recovery	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Beuchat et al. [36]	202	Retrospective analysis of prospective registry data, observational Investigated the relationship between standardized EEG patterns and other outcome predictors at different temperatures, during and after TTM	On day 1 after TTM of 73 patients with a highly malignant EEG, 40.3% had absent PLR on clinical examination, while only 7.3% of 125 patients with a non highly malignant EEG had absent PLR on clinical observation ($p < 0.001$) % change in PLR measured on day 1 after TTM showed that patients having a highly malignant EEG had a lower % change PLR versus patients without a highly malignant EEG (16.6 ± 10.4 vs. 23.1 ± 13.0, $p < 0.001$) On day 1 after TTM, 97.2% of the 38 patients who had a benign EEG pattern had present PLR on clinical observation, while only 76.6% of patients with a non benign pattern had present PLR ($p = 0.005$) The % change in PLR measured on day 1 after TTM showed that patients having a benign EEG had a higher %change PLR versus patients with a non-benign EEG (26.6 ± 14.2 vs. 19.6 ± 11.8, $p < 0.023$) On day 2 after TTM, of 41 patients with a Highly malignant EEG, 47.5% had absent PLR on clinical examination, while only 19.9% of 149 patients with a non-highly malignant EEG had absent PLR on clinical observation ($p < 0.001$) The % change in PLR measured on day 2 after TTM showed that patients having a highly malignant EEG had a lower %change PLR versus patients without a highly malignant EEG (12.8 ± 7.8 vs. 22.1 ± 12.6, $p < 0.001$) Day 2, 96.7% of the 63 patients who had a benign EEG pattern had present PLR on clinical observation, while only 73.8% of patients with a non-benign pattern had present PLR ($p \leq 0.001$) The % change in PLR measured on day 2 after TTM showed that patients having a benign EEG had a higher %change PLR versus patients with a non-benign EEG (25.2 ± 14.2 vs. 17.7 ± 10.4, $p < 0.001$) Study showed limited correlation between benign EEG on day 1 and PLR, but correlation between highly malignant patterns and PLR were stronger, which supports the indication that PLR was predictive of poor outcome, but was less accurate for favorable outcomes	Did not consider amount of sedation during EEG recordings Not blinded, leading to a possible self-fulfilling prophecy	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Behrends et al. [37]	30	Case series Examined whether the PLR could be objectively measured during cardiopulmonary resuscitation, and whether the PLR was associated with outcome	PLR was detectable in 25 of the 30 (83%) patients during CPR by serial measurements: 9 had PLR present at all times during CPR 4 had intact PLR at outset of CPR that was subsequently lost 8 had no initial PLR but had recovery of PLR in less than 5 min 4 had no initial PLR but had recovery of PLR in greater than 5 min 7 patients had the best neurological outcome 3 days post arrest (CPC scale 1, 2, or 3). Of those, 3 had PLR present throughout CPR, while 4 had initial absence of PLR that returned within 5 min of the start of CPR Typically, these patients had increasing amplitudes of PLR throughout CPR Of the 10 patients who did not survive the code, 5 had absence of PLR at all times during CPR and 5 had initial presence of CPR that became absent over the course of CPR with a decreasing trend in PLR Study shows that in patients who survived resuscitation for 3 days, the presence of a PLR during resuscitation was an excellent predictor for a favorable neurological outcome ($p = 0.002$) Showed that presence of PLR during CPR detected by pupillometry was able to predict early survival from resuscitation, $p = 0.0002$	Small sample size, case series Were not able to associate return of PLR during resuscitation with other measures that can be used to determine effectiveness of CPR	Very Low
Heimburger et al. [38]	82	Prospective observational study Investigated performance of quantitative pupillometry and transcranial doppler to predict outcomes after CA during use of TH	27 patients with good neurological outcome (CPC 1–2) had higher amplitude PLR than the 55 patients with poor neurological outcome (CPC 3–5) both at day 1 (13% vs. 8%, $p < 0.001$) and at day 2 after 24 h of therapeutic hypothermia and sedation (17% vs. 8%, $p < 0.001$) AUC–ROC curves at days 1 and 2 were 0.76 and 0.82, respectively. The best cutoff values for predicting poor 3-month outcome were PLR < 9% and < 11%, respectively, for days 1 and 2 PLR amplitude of < 7% on day 2 predicted poor outcome with 100% specificity and 42% sensitivity Concludes that quantitative pupillometry may be useful in prognosticating poor outcome in the early phase of post-CA management	Not blinded, leading to a possible self-fulfilling prophecy External validation of a previous single-center cohort study PLR amplitude threshold of < 7% to have 100% specificity had a 95% CI of 14%, exceeding what has been recommended to consider robustness of a predictor (95% CI of < 5%)	Low
Sawyer et al. [40]—abstract	55	Prospective, observational study Investigated whether quantitative pupillometry could provide early prognostic information post-CA in patients treated with TTM	37 patients had a prediction of poor outcome based on peak neuron specific enolase levels (AUC = 0.90, $p < 0.001$) and malignant EEG features (AUC = 0.8, $p < 0.001$) within 72 h of ROSC Pupillometry values of NPi (AUC = 0.70, $p = 0.003$), 6 h CV (AUC = 0.73, $p = 0.002$), and % constriction (AUC = 0.68, $p = 0.01$) were identified as very early predictors of poor outcomes Very early monitoring post-CA with these pupillometry values appears to accurately predict poor outcome	Small sample size, abstract only No discussion of limitations	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Riker et al. [40]—abstract	55	Prospective, observational study Investigated whether quantitative pupillometry could provide prognostic information post-CA in patients treated with TTM	37 patients had poor outcome at discharge At first reading post ROSC, 6 patients had unilateral NPi equaling 0, and 4 patients had bilateral NPi equaling 0. None of these patients survived 15 patients who had poor outcomes had an initial NPi of < or = to 3 bilaterally, while 5 patients with poor outcomes had an initial NPi of < or = to 3 unilaterally In 18 of 20 patients, bilateral NPi was < or = to 3 when measured 6 h after ROSC. 2 of 20 patients had unilateral NPi < or = to 3 20 patients with poor outcomes developed an NPi of 0 during TTM, a median of 6.4 h after ROSC One patient had a good outcome, with an NPi of 3.3–4.0 in preceding assessments (1.8–4.4 h prior)	Small sample size, abstract only No discussion of limitations No p values or associations given	Low
Sawyer et al. [41]—abstract	51	Prospective, observational study Determine whether using infrared pupillometry to measure NPi and PD can provide early, accurate prognostic information in comatose adult survivors of CA treated with TTM	Initial NPi was lower in poor outcome patients compared to good outcome patients (3.3 vs. 3.9, $p = 0.005$) measured a median of 4.5 h after ROSC NPi started above but dropped below 3 in a higher % of poor outcome patients compared with good outcome patients (77% vs. 37.5%, $p = 0.015$) and NPi went to 0 in 51% of poor outcome patients but only 6% of good outcome patients ($p = 0.005$) ROC curves showed initial NPi predicted poor outcome better than PD (AUC = 0.78 vs. 0.61, $p = 0.016$) Concluded low NPi predicted poor outcome 4–6 h after ROSC and NPi dropped to abnormal levels (< 3) and 0 more often in patients that had poor outcomes	Small sample size, abstract only No discussion of limitations	Low
Reynolds et al. [42] – abstract	173	Prospective, observational cohort study Demonstrated the feasibility of pre-hospital pupillometry to quantify/qualify the PLR during resuscitation, guide efforts, and provide early neuroprognostication	Of 39 patients admitted to the hospital, 7 survived to discharge with 6 following commands and 5 with a modified Rankin Scale of 0–3. A median of 7 readings was attempted per person 39% had usable data, and 74% had > or = to 1 usable reading. Only 15% of subjects had PLR during resuscitation A best NPi of > 4.0 was seen in 92% of those who could follow commands (AUC 0.69) A best NPi of > 4.5 was seen in 98% with favorable Modified Rankin Scale and CPC (AUC 0.70) Although rare, normal PLR had high overall classification accuracy for following commands, and strong likelihood ratios for neurologic outcome	Abstract only No discussion of limitations Only a small number of patients had detectable PLR Small sample size of patients who were admitted to the hospital	Low
Suys et al. [43]—abstract	24	Prospective, observational study Examined the value of quantitative PLR to predict outcomes in comatose post-CA patients treated with TH	Quantitative PLR was strongly associated with survival—median left eye PLR% variation in patients who survived was 14%, median left eye PLR in patients who did not survive was 5.5% ($p < 0.0001$) Quantitative PLR was strongly associated with 3-month neurological outcomes; good outcomes (CPC 1 and 2) had a median PLR% variation of 14%, while poor outcomes (CPC 3–5) had a median PLR% variation of 5.5% ($p < 0.0001$) Similar results were obtained in PLR measurements of the right eye PLR% variation > 10% was 100% predictive of patient prognosis Concluded that quantitative PLR appears highly accurate and superior to standard clinical examinations of motor response and brainstem reflexes in predicting outcome in post-CA comatose patients	Small sample size, abstract only No discussion of limitations	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Park et al. [44]	117	Prospective, observational study Evaluation of the clinical utility and validity of automated pupillometry to assess patients with acute brain lesions	NPi values were not statistically different between age groups or intensity of illumination There is a definite difference in initial NPi values between "poor" (GCS of < 3 at 1-month follow-up) and "favorable" (GCS of > or = to 3 at 1 month follow-up) prognosis groups (mean ± SD) (0.88 ± 1.68 vs. 3.89 ± 0.97, $p = 0.001$) With an NPi cutoff value of 3.4, the initial NPi value of automated pupillometer had 86% sensitivity and 84.6% specificity in predicting clinical outcome 1 month after acute brain injury	Did not consider delayed clinical deteriorations or neurosurgical interventions in the evaluation of outcome prediction Did not consider drug interactions, such as sedatives	Low
Shoyombo et al. [23]	1617	Prospective analysis of registry data, observational Examined the prevalence of brisk CV in cases with normal NPi in a neurocritical care setting	CV greater than or equal to 0.8 is associated with a high likelihood of observing a normal (> or = to 3) NPi in both the left eye (OR 12.6, 95% CI 11.8–13.5) and right eye (OR 9.6, 95% CI 8.9–10.3) CV < 0.8 was associated with high likelihood of having an abnormal (< 3) NPi in the left eye (OR 12.6, 95% CI 11.8–13.5) and right eye (OR 9.6, 95% CI 8.9–10.3) Slow CV (< 0.8 mm/s) was associated with a low likelihood of having a normal NPi in both the left eye (OR 0.08, 95% CI 0.07–0.09), and right eye (OR 0.1, 95% CI 0.1–0.1) Brisk CV (≥ 0.8 mm/s) was associated with low likelihood of having an abnormal NPi (< 3) in both the left eye (OR 0.08, 95% CI 0.07–0.09), and right eye (OR 0.1, 95% CI 0.1–0.1) A weak association between NPi and CV for both the left ($r^2 = 0.068$) and right ($r^2 = 0.052$) eyes ($p < 0.001$) was found using simple regression Increasing pupil size and the % change in pupil size were predictive of CV ($r^2 = 0.72$ and $r^2 = 0.457$, $p < 0.001$; respectively) in the left eye and in the right eye ($r^2 = 0.725$ and $r^2 = 0.379$, $p < 0.001$; respectively) 30.9% of observations had either one or both eyes showing normal NPi with slow CV, or abnormal NPi with brisk CV The finding that a briskly reactive pupil is insufficient to conclude that the PLR is normal is significant Practitioners performing manual pupillary examinations may equate brisk CV with a normal examination and miss subtle changes in the PLR The sensitivity of automated pupillometry to changes in the PLR can prevent these errors CV–NPi relationship has the potential to be an intriguing noninvasive biomarker	Possible confounding influence based on the repeated measures, although this factor was addressed when carrying out the regression analysis Heterogeneous pathologies that may be more or less susceptible to PLR changes Variations in lighting No recorded variables to control for optic nerve damage	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Yan et al. [19]	183 (42 controls)	Prospective, observational study To assess the pupillary response, as measured by automated pupillometer and manual pupillometer, in clinical liver transplantation settings	183 liver transplant patients with varying degrees of hepatic encephalopathy, 22 healthy volunteers, and 20 patients with cirrhosis but no encephalopathy were examined No difference between manual and automated pupillometry when looking at inter-examiner consistency for pupil reactivity with brisk reactivity Patients with absent pupil reactivity and sluggish pupil reactivity had a smaller inter-examiner disagreement for automated than manual pupillometry, respectively (4.5% vs. 27.3%, $p < 0.05$ and 4.5% vs. 31.8%, $p < 0.05$) No pupillary reactivity was detected by automated pupillometry in 4 patients, 3 of which died shortly after liver transplant with good functional grafts, and 1 that was excluded from transplantation All patients who had a detected pupil response by automated pupillometry did not have short-term death 3 patients with a delayed recovery of pupillary reflexes developed demyelinating encephalopathy or dementia, suggesting that pupillary abnormalities, such as persistent diminished reactivity and prolonged latency, may strongly indicate potential neurological problems	Did not control for lighting during manual and automated pupillometry Pupils were measured before the operation, during the operation with deep sedation, and at withdrawal of anesthesia. No information is given in regards to type or amount of anesthesia given, or the exact timing of pupillometry measurements Observational and not blinded when examining liver transplantation patients following surgery	Low
Couret et al. [20]	59 (200 controls)	Prospective, double-blinded observational study Compared automated pupillometry with standard clinical pupillary examination for brain-injured patients	19% rate of discordance in pupil size measurements between manual examination by nurses and automated pupillometry for pupils between 2 and 4 mm in size; increased to 39% for pupils less than 2 mm Trained neurocritical care nurses did not detect 15/30 of cases of anisocoria and wrongly detected 16 cases of anisocoria Global error rate for pupillary light reflex by manual examination was 18% Spearman's coefficient of correlation between manual and automated examination was 0.75 (95% CI 0.71–0.79), $p < 0.001$ for all pupil sizes, but decreased to 0.39 (95% CI 0.15–0.59), $p = 0.002$ for pupils less than 2 mm, 0.44 (95% CI 0.33–0.54), $p < 0.001$ for pupils 2–4 mm in size, and 0.37 (95% CI 0.19–0.51), $p = 0.001$ for pupils greater than 4 mm in size Accuracy of standard practices in pupillary monitoring by nurses is poor and can be improved with automated pupillometry	Penlight in manual pupillometry may have given variable amounts of illumination Manual pupillometry was done by nursing staff, while physicians performed automated pupillometry Trial was not designed nor powered to study the clinical impact of automated pupillometry on patient outcomes	Low
Meeker et al. [11]	20	Prospective, observational study Determine the accuracy and reliability of an automated pupillometer compared to the standard manual examination to assess the usefulness of automated pupillometry in the critical care setting	Median absolute error in pupillary size measurements using manual examination is over twice as large as the median absolute error in pupillary size measurements made with an automated pupillometer (0.54 mm, 95% CI 0.51–0.62 vs. 0.23 mm, 95% CI 0.20–0.31) Spearman correlation coefficient between error in pupil size and pupil size was 0.27 ($p = 0.026$) for the manual examination and 0.33 ($p = 0.0044$) for the automated pupillometer Disagreement over pupillary reactivity was much more common between observers performing manual examination when compared to using automated pupillometry (39%, CI 28–52% vs. 1.4%, CI 0–7.6%) The disagreement among manual measurements was > 38% (CI 25–51%) compared to automatic measurements ($p < 0.0001$) Data supports the conclusion that there is lower inter-observer discrepancy and increased agreement in pupillary measurements with use of automated pupillometry	Small sample size Observational study Unable to obtain 5 sets of measurements due to periorbital edema or chemosis	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Zhao et al. [21]	20	Prospective, observational study To determine the inter-device reliability of NPi-100 pupillometers (NeuroOptics, Inc.)	210 paired pupillometry measurements obtained by two independent investigators each using a different NPi-100 pupillometer No statistically significant difference found between the two pupillometers when measuring: Mean maximum pupil size at rest for the left eye (3.8 (1.1 SD) vs. 4.0 (1.6 SD), $p=0.27$) and right eye (3.6 (1.1 SD) vs. 3.8 (1.1 SD), $p=0.74$) Minimum pupil size during light stimulation for the left eye (2.8 (1.2 SD) vs. 3.0 (1.5 SD), $p=0.64$) and right eye (2.6 (1.0 SD) vs. 2.6 (0.6 SD), $p=0.44$) Mean pupil reactivity for the left eye (3.9 (1.2 SD) vs. 3.9 (1.4 SD), $p=0.36$) and right eye [4.2 (1.0 SD) vs. 4.3 (0.8 SD), $p=0.82$] Cohen's kappa assessments (*k*) for pupil size and reactivity showed almost perfect agreement between the two pupillometers for: Maximum pupil size ($k=0.97$ left eye) and ($k=0.91$ right eye) Minimum pupil size ($k=0.96$ left eye) and ($k=0.98$ right eye) Pupil reactivity ($k=0.99$ left eye) and ($k=0.90$ right eye) when non-reactive pupils were included in the analysis Concludes that there is extremely high inter-device/inter-rater reliability with use of NPi-100 automated pupillometer	Small sample size Did not collect specific patient variables that may have impacted the results, including age, presence of cataract, etc Possibility of a learning curve when using the device so that there will be fewer dropped values as examiners become more experienced Assessment of agitated or confused patients was challenging	Low
Olson et al. [14]	127	Prospective, single-blinded observational study Examined inter-rater reliability of pupil examination findings between two practitioners and an automated pupillometer	Inter-rater reliability between practitioners performing manual pupillary assessments was moderate for pupil size (kappa's coefficient (k) = 0.54, 95% CI 0.50–0.57) Agreement on pupil size between practitioners and pupillometer was fair ($k=0.29$, 95% CI 0.27–0.32 and $k=0.31$, 95% CI 0.28–0.34 for the first and second practitioners, respectively) Low agreement on detection of anisocoria between practitioners and pupillometer 33.3% of pupils scored as non-reactive by practitioners were scored as non-reactive by pupillometry Practitioner agreement on pupil reactivity scored as fixed (non-reactive), sluggish, or brisk was fair ($k=0.40$, 95% CI 0.36–0.44) Suggests that the use of automated pupillometry can standardize the assessment of pupillary function and provide higher reliability	Diverse group of practitioners (registered nurses, nurse practitioners, neurologists, neurosurgeons, and resident physicians) No standardization of light sources and environmental conditions Practitioners were not completely blinded to the findings of the second practitioner and automated pupillometer Possible that practitioners may have tried harder than normal to obtain a correct assessment of pupil size An automated pupillometer reading could not be obtained 5.9% of the time. This was higher in the first half of the study, suggesting there may be an operator learning curve	Low
Lukaszewicz et al. [27]	37	Prospective, observational study Evaluated the pupillary response to a light stimulus before noxious procedures using an automated pupillometer as a method to predict pain during the procedure and to assess adequacy of analgesia	% variation in pupil size of > 19% predicted the presence of pain during a dressing change, as assessed by a Behavioral Pain Scale score of > 3 with a sensitivity of 100% (95% CI 100–100%) and a specificity of 77% (95% CI 54–100%) Patients with largest pupil diameter and greatest variation were those who presented pain behavior during the noxious procedure, possibly due to insufficient analgesia Suggests that pupillometry may be a useful tool to determine whether patients who are unable to verbally communicate need adjustments of their analgesia level prior to a noxious procedure	No sample size calculation was performed, limiting the precision of the study findings	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Li et al. [31]	48	Prospective, descriptive, two-site study Described cardiovascular, pupil reactivity, and behavioral responses between noxious and non-noxious procedures in sedated, ventilated cardiac surgery ICU patients	Significant differences between noxious and non-noxious procedures when examining pupil size ($F(3, 41) = 5.65$, $p < .001$) Significant changes in pupil size (+ 16%) were observed when comparing baseline to noxious stimulation	Small sample size, with only cardiac surgery patients Opioid analgesics were given to patients based on nurses' discretion, possibly affecting pupillary responses Did not control for other influencing factors including hypothermia, residual effects of anesthesia, and other various ICU therapies	Low
Wildemeersch et al. [32]	40	Single-center prospective cohort, observational study Evaluated use of two nociceptive reflex testing devices, PDR and nociception flexion reflex, as tools for objective pain measurement in mechanically ventilated patients	PDR was elicited in 100% of patients Showed that automated pupillometry in unconscious patients is both feasible and fast When generating a pupillary pain index score, automated pupillometry is able to indicate the level of analgesia	The pupillometer uses an inbuilt measurement, the pupillary pain index, but no normative data currently exist for normal reflex ranges in critically ill patients	Low
Gaillard et al. [30]—abstract	41	Prospective, interventional study, observational Evaluated whether measurement of PDR during tetanic stimulation by pupillometry predicts insufficient analgesia prior to nursing care in critically ill, sedated, intubated, and mechanically ventilated patients	PDR was not associated with pain during nursing, including giving doses of sedation and analgesia AUC of PDR at different stimulation levels did not exceed 0.6, and no difference existed between different stimulation intensities The PPI score was not better (4.1[3.2–5] vs. 4.9[4.5–5.4]) for painful or not ($p = 0.10$) Suggests that pupillometry cannot predict insufficient analgesia prior to a nursing care in surgical ICU patients	Abstract only Authors suggest that the high heterogeneity of diseases among patients (peritonitis, mediastinitis, multiple trauma, etc.) may affect results, as the same nursing care may induce highly variable degrees of pain depending on the patient's condition Exclusion criteria included those with a pacemaker, TBI, or spinal cord injury	Low
Taylor et al. [18]	26 (200 healthy controls)	Prospective Analyzed the ability to detect pupillary changes that indicate a rise, or impending rise, in ICP and to provide increased precision, reliability, and reproducibility compared with the manual pupillary examination	8 of 26 patients with head injuries were found to have elevations of ICP above 20 mmHg and pupillary dynamics remained normal 13 patients with midline shift greater than 3 mm and ICP elevations above 20 mmHg for 15 min were found to have a reduction in CV on the side of the mass effect to below 0.6 mm/s (51% of 156 paired observations) Authors suggest that reduction in CV to below 0.8 mm/s is suggestive of increases in brain volume, and when CV falls below 0.6 mm/s, there is a likelihood that ICP, if not already elevated, will become elevated within 15–30 min in patients with significant mass effect 5 patients with diffuse brain swelling but no midline shift showed no reduction in CV until the ICP exceeded 30 mmHg Asymmetry of pupillary size > 0.5 mm was observed in < 1% of the 200 controls. Rarely seen in patients with head injuries unless the ICP exceeded 20 mmHg	Small sample size, observational study No association statistics Not blinded	Low
Giede-Jeppe et al. [25]–abstract	31	Prospective, observational study Identified pupillary parameters associated with ICP crisis in neurocritical care patients	79 ICP crises were detected in 9 of 31 patients. ROC showed a negative association between NPi, maximal CV, and CV, and the detection of ICP crisis NPi < 4.15 at the time of ICP measurement was associated with a 7.7 fold higher rate of ICP crisis compared to NPi > 4.15 ($p < 0.001$)	Small sample size, abstract only No discussion of limitations	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Larson and Muhiudeen [22]	16	Case series Evaluated ability to detect subtle pupillary changes that may be missed with manual examination	Infrared pupillometry was conducted on 16 patients that had an absence of light reflex on routine penlight examination: 7 with confirmed brain death and 9 in a coma without brain death (GCS < or = to 5) No light reflex detected on the 7 patients with confirmed brain death Intact light reflex in 4 of the 9 patients with coma but without brain death when using infrared pupillometry The manually undetectable reflex was characterized by low amplitude and low maximum CV, suggesting that this midbrain reflex may be present and demonstrated with infrared pupillometry when not detected by routine clinical methods	Small sample size, case series No association statistics are provided	Very low
Rouche et al. [28]	31	Prospective, monocentric observational study Examined automated pupillometric video as a noninvasive, simple, and reproducible technique to evaluate the depth of sedation in ICU patients, as compared to the bispectral index (BIS)	Patients classified into three groups: BIS < 40 indicated heavy sedation, 40 ≤ 60 indicated acceptable sedation, and BIS > 60 indicated light sedation Statistically significant difference in V_{max} (mm/s) (1.14 vs. 1.35, $p < 0.0001$) and variation in PD (mm) (0.3 vs. 0.4, $p < 0.0001$) between heavy sedation and acceptable sedation groups Statistically significant difference in V_{max} (mm/s) (1.14 vs. 1.40, $p < 0.0001$) and variation in PD (mm) (0.3 vs. 0.43, $p < 0.0001$) between heavy sedation and light sedation groups Concluded that V_{max} and variation in PD measured by video pupillometer were useful in the evaluation of sedation in the ICU compared with BIS	Small sample size Exclusion criteria included neurological pathologies such as severe head trauma, subarachnoid hemorrhage, stroke, intracerebral hemorrhage, or multiple sclerosis Exclusion criteria included ophthalmological pathologies such as conjunctivitis and high myopia	Low
Ong et al. [24]—abstract	100	Prospective, observational study Determined pupil characteristics in critically ill population	Increased asymmetry in both pupil size ($p = 0.002$) and dilation velocity ($p = 0.02$) was associated with increased ICP The presence of low NPis in more than 10% of total pupil measurements was associated with death at discharge ($p = 0.02$) Study concludes that pupillary metrics in critically ill patients correlates with ICP	Small sample size, abstract only No discussion of limitations No association statistics are provided	Low
Paulus et al. [29]	34	Prospective, non-interventional study Evaluated the PDR during tetanic stimulation to predict insufficient analgesia before nociceptive stimulation of deeply sedated surgical ICU patients	PDR with 10 mA, 20 mA, and 40 mA stimulation was higher in patients with insufficient analgesia ($p < 0.01$) Pupil diameter variations during a 10 mA, 20 mA, and 40 mA tetanic stimulation to predict insufficient analgesia during endotracheal suctioning were 1, 5, and 13%, respectively AUC/ROC were 0.70 (95% CI 0.54–0.85), 0.78 (95% CI 0.61–0.91), and 0.85 (95% CI 0.721–0.954) for a 10 mA, 20 mA, and 40 mA tetanic stimulation, respectively	Small sample size, prospective observational study Not blinded, leading to possible bias	Low

Table 1 (continued)

References	*n*	Description of study	Main findings	Limitations	GRADE
Natzeder et al. [26]	18	Retrospective analysis of prospective registry data, observational Examined different aspects of NPi and their relation to clinical severity and outcome in patients with aSAH using serial NPi measurements	Statistically significant inverse correlation between NPi and ICP (Spearman $r = -0.551$, $p < 0.001$) Mean NPi was lower in clinically severe (WFNS 4–5) vs. non-severe (WFNS 1–3) aSAH (mean ± SE) (3.75 ± 0.40 vs. 4.56 ± 0.06, $p = 0.171$) Pathologic NPi values were more frequent in clinically severe (WFNS 4–5) vs. non-severe (WFNS 1–3) aSAH (mean ± SE) (16.3% ± 8.8% vs. 0.0% ± 0.0%, $p = 0.002$) Mean NPi was lower in patients with unfavorable (GOS 1–3) vs. favorable (GOS 4–5) outcomes at discharge (mean ± SE) (3.64 ± 0.48 vs. 4.50 ± 0.08, $p = 0.198$) Pathologic NPi values were more frequent in patients with unfavorable (GOS 1–3) vs. favorable (GOS 4–5) outcomes at discharge (mean ± SE) (19.2% ± 10.6% vs. 0.7% ± 0.6%, $p = 0.017$) Subgroup analysis of patients with clinically severe aSAH (WFNS 4–5) showed a significantly lower mean NPi for patients who died compared to those who survived (2.5 ± 1.2 vs. 4.2 ± 0.2, $p = 0.041$) Concluded that NPi reflects the clinical severity of aSAH and that there is an association between pathologic NPi values and poor clinical outcome	Small sample size Failure to include confounders, such as ambient light Substantial heterogeneity of the assessed time periods Continuous long-term (≥ 10 days) NPi measurements were only available for clinically severe patients Failure to consider administration of concurrent medications including opioids and anesthetics/sedatives	Low
Ong et al. [45, 48]	72	Prospective, observational study Evaluated whether the effects of osmotic therapy administration can be measured by repeated quantitative pupillary measurements	Statistically significant improvement in NPi was seen in patients with abnormal NPi (< 3) prior to osmotic therapy when comparing measurements before versus after medication administration (median (IQR)) [2.4 (1.75–2.65) vs. 3.0 (1.9–3.45), $p < 0.0004$] Statistically significant improvement in NPi was also seen in patients with normal NPi (≥ 3) prior to osmotic therapy when comparing measurements before versus after medication administration (median (IQR)) [4.4 (3.8-4.7) vs. (4.5 (4.0–4.7), $p < 0.0322$] Results remained significant for the total patient cohort ($p = 0.0168$) and for patients with abnormal NPi (< 3) prior to therapy initiation ($p = 0.0235$) when controlling for other interventions to reduce ICP Suggests improvement in pupillary reactivity measured by quantitative pupillometry could serve as a noninvasive biomarker of reduction in cerebral edema, intracranial pressure, and/or displacement of midbrain and medullary structures after osmotic therapy	Small sample size among patients with poor pupil reactivity or with a single osmotic therapy, observational study only Heterogeneous diagnoses and injury location Inability to measure the dose-dependent effects continuous sedative and blood pressure medication escalation may have Failure to record other factors that can affect pupillary responsiveness Measures of other interventions for elevated ICP were collected retrospectively	Low

aSAH aneurysmal subarachnoid hemorrhage, *AUC* area under the curve, *BIS* bispectral index, *CA* cardiac arrest, *CI* confidence interval, *CPC* cerebral performance category, *CPR* cardiopulmonary resuscitation, *CV* constriction velocity, *EEG* electroencephalogram, *GCS* Glasgow Coma Scale, *GOS* Glasgow Outcome Scale, *ICP* intracranial pressure, *ICU* intensive care unit, *NPi* neurological pupil index, *PD* pupil diameter, *PDR* pupillary dilation reflex, *PLR* pupillary light reflex, *ROC* receiver operating characteristics, *ROSC* return of spontaneous circulation, *SSEP* somatosensory evoked potentials, *TBI* traumatic brain injury, *TTM* target temperature management, *TH* therapeutic hypothermia, *WFNS* World Federation of Neurological Surgeons subarachnoid hemorrhage scale

lower CV values (sluggish pupils), as would be expected. 30.9% of patients had either one or both eyes showing normal NPi with slow CV, or abnormal NPi with brisk CV, mismatches that are often missed on manual pupillary examination.

Detection of Pupillary Changes that Indicate a Rise, or Impending Rise, in Intracranial Pressure

The ability of automated pupillometers to detect pupillary changes that indicate a rise, or impending rise, in ICP was evaluated by four studies included in this review [18, 24–26]. Taylor et al. [18] showed that pupillary size asymmetry detected by automated pupillometry of at least 0.5 mm was present in 81% of observations when ICP rose above 30 mmHg. Similarly, Giede-Jeppe et al. [25] showed an association between pupillary index technology and increased ICP as an NPi < 4.15 at the time of ICP measurement was associated with a 7.7-fold higher rate of ICP crises when compared to an NPi > 4.15. Additionally, Natzeder et al. [26] confirmed prior findings of a statistically significant inverse correlation between NPi and ICP (Spearman $r = -0.551$, $p < 0.001$) using data from patients that had undergone continuous ICP monitoring.

Detection of Level of Analgesia and Depth of Sedation

There are six studies included in this review that assess the ability of automated pupillometry to detect the level of analgesia or depth of sedation in critically ill patients [27–32]. Lukaszewicz et al. [27] examined patients who were unable to communicate verbally and found that a percentage variation in pupil size (> 19%) during a noxious stimulus (i.e., dressing change) was predictive of the presence of pain as determined by a Behavioral Pain Scale score > 3 with 100% sensitivity and 77% specificity. Rouche et al. [28] compared maximum contraction velocity of the pupil (V_{max}) and variation in pupil diameter (PD) between three groups based on evaluation of bispectral index (BIS): heavy sedation (< 40), acceptable sedation (40–60), and light sedation (> 60). They found a statistically significant difference in V_{max} (1.14 mm/s vs. 1.35 mm/s, $p < 0.0001$) and variation in PD (0.3 mm vs. 0.4 mm, $p < 0.0001$) between heavy sedation and acceptable sedation groups. There was also a statistically significant difference in V_{max} (1.14 mm/s vs. 1.40 mm/s, $p < 0.0001$) and variation in PD (0.3 mm vs. 0.43 mm, $p < 0.0001$) between heavy sedation and light sedation groups.

Paulus et al. [29] evaluated the performance of the pupillary dilatation reflex (PDR), an autonomic response that results from a noxious stimulus, in predicting insufficient analgesia before endotracheal suctioning of deeply sedated mechanically ventilated ICU patients by applying tetanic stimulations of 10, 20, and 40 mA to elicit the PDR. The areas under the receiver operating characteristic (ROC) curve for predicting insufficient analgesia were 0.70 (95% CI 0.54–0.85), 0.78 (95% CI 0.61–0.91), and 0.85 (95% CI 0.721–0.954) with 10, 20, and 40 mA tetanic stimulations, respectively. However, Gaillard et al. [30] performed a similar study in sedated and mechanically ventilated surgical ICU patients with tetanic stimulations of 5, 10, 20, 40 and 60 mA and found no difference in the areas under the ROC curves between different intensity levels, and PDR at different stimulation levels never exceeded 0.6.

Utility as a Prognostic Indicator

Of the 30 studies included in this review, 14 explore the ability of the automated pupillometer to be used as a prognostic indicator [24, 26, 33–44]. Tamura et al. [33] showed that automated quantitative PLR values were consistently higher in survivors of CA within the first 72 h of return of spontaneous circulation (ROSC) compared to non-survivors at 90 days. PLR value was associated with 90-day survival ($p < 0.001$). PLR values were also consistently higher in patients with a good neurological outcome determined by a cerebral performance category (CPC) of 1 or 2 compared to those with poor neurological outcomes (CPC 3–5) at 90 days. PLR value was associated with 90-day favorable neurological outcomes ($p < 0.001$). ROC curve analysis for the comparison of area under the curve (AUC) values at each measurement time point (0, 6, 12, 24, 48, and 72 h after ROSC) showed that 0-h PLR value was the best predictor of 90-day survival with an AUC value of 0.82 using a PLR cutoff value of 3%. Additionally, 0-h PLR value was the best predictor of good neurological outcome at 90 days with an AUC value of 0.84 and PLR cutoff value of 6%.

Similarly, Solari et al. [34] were the first to use a blinded approach to analyze the value of quantitative automated pupillometry to predict neurologic recovery in CA. The blinded approach was taken to limit "self-fulfilling prophecy." A total of 103 comatose adult patients who were unconscious 48 h after CA underwent repeated measurements of quantitative PLR using an automated pupillometer. It was discovered that a quantitative PLR < 13% at a relatively early stage after CA (48 h) was 100% predictive of mortality, irrespective of the amount of sedatives, analgesics, and vasopressors.

The prognostic value of automated pupillometry has also been demonstrated in clinical conditions other than CA. Park et al. [44] evaluated the utility of automated pupillometry to predict clinical outcomes in patients with acute brain lesions. They showed that there is a definite difference in initial NPi values between patients with poor neurological outcomes as determined by a Glascow Outcome Scale (GOS) < 3 and those with favorable (GOS ≥ 3) outcomes (mean ± SD) (0.88 ± 1.68 vs. 3.89 ± 0.97, $p = 0.001$) at 1-month follow-up from injury. With an NPi cutoff value of 3.4, the initial NPi value of the automated pupillometer had 86% sensitivity and 84.6% specificity in predicting the clinical outcome at 1 month after the acute brain injury. Furthermore, Natzeder et al. [26] demonstrated the utility of automated pupillometry as a prognostic indicator in aSAH. They found that mean NPi tended to be lower in patients with unfavorable (GOS 1–3) compared to favorable (GOS 4–5) outcomes at the time of discharge (mean ± SE) (3.64 ± 0.48 vs. 4.50 ± 0.08, $p = 0.198$) and pathologic NPi values were recorded more frequently in patients with unfavorable compared to favorable outcomes (19.2% ± 10.6% vs. 0.7% ± 0.6%, $p = 0.017$). Subgroup analysis of patients with clinically severe aSAH as determined by a World Federation of Neurological Surgeons (WFNS) grade of 4–5 showed a significantly lower mean NPi for patients who died compared to those who survived (2.5 ± 1.2 vs. 4.2 ± 0.2, $p = 0.041$).

Estimation of Clinical Severity in Aneurysmal Subarachnoid Hemorrhage

The study by Natzeder et al. [26] examined the ability of quantitative automated pupillometry to estimate the clinical severity of aSAH. Although not statistically significant, they found that mean NPi tended to be lower in patients with clinically severe (WFNS 4–5) compared with non-severe (WFNS 1–3) aSAH (mean $\pm$ SE) (3.75 $\pm$ 0.40 vs. 4.56 $\pm$ 0.06, $p = 0.171$). A statistically significant difference was found between the frequency of pathological NPi values in clinically severe (WFNS 4–5) and non-severe (WFNS 1–3) aSAH (16.3% $\pm$ 8.8% vs. 0.0% $\pm$ 0.0%, $p = 0.002$).

Utility as a Noninvasive Monitor of Response to Osmotic Therapy

Ong et al. [45] evaluated the utility of quantitative automated pupillometry as a noninvasive biomarker to monitor reduction in ICP after administration of an osmotic agent in patients admitted to the neuroICU with increased ICP and brain herniation. They showed that there was a statistically significant improvement in NPi within 2 h of administration of either 20% mannitol or 23.4% hypertonic saline in patients with abnormal NPi (<3) prior to medication delivery (median [IQR]) [2.4 (1.75–2.65) vs. 3.0 (1.9–3.45), $p < 0.0004$]. This improvement was also seen in patients with normal NPi (>3) prior to receiving osmotic therapy [4.4 (3.8–4.7) vs. 4.5 (4.0–4.7), $p < 0.0322$]. Results remained significant for the total patient cohort ($p = 0.0168$) and for patients with abnormal NPi (<3) prior to therapy initiation ($p = 0.0235$) when controlling for other interventions to reduce ICP including cerebrospinal fluid diversion, blood pressure management strategies, initiation or increase in anesthetic and analgesic agents, and hyperventilation.

Discussion

Assessment of primary outcomes confirms that the automated pupillometer has utility in the care of critically ill patients with neurological impairment. The importance of serial pupillary examinations to a thorough neurologic assessment is well established [9]. However, the traditional approach of using manual serial pupillary examinations performed by trained healthcare professionals has come under scrutiny due to its inherent subjectivity demonstrated by low intra- and inter-observer reliability and errors in detecting a light reflex in very small and dilated pupils [12–14]. Automated pupillometry devices provide an objective measure of pupillary size and reactivity [15]. We conducted a literature review to explore the evidence assessing the usefulness of automated pupillometry in the care of critically ill patients with neurological impairment. After an exhaustive review, 30 records of original studies with human subjects were identified that assessed outcomes of the use of automated pupillometry in a critical care setting. Although a variety of pupillometers from common commercial brands were used in the studies that we reviewed, including NeurOptics® and IDMed®, the basic functionality was the same. Each pupillometer was capable of assessing multiple variables commonly associated with the PLR including pupillary size, constriction velocity, dilation velocity, and latency period from light exposure to start of constriction [15]. However, it is important to note that although a study examining inter-device reliability of the NeurOptics® NPi™-100 Pupillometer has been published [21], to date there has been no head-to-head trial comparing the relative reliability of different brands and models of automated pupillometers.

Summary of Primary Outcomes Data

Data extracted from studies evaluating the increased precision, reliability, and reproducibility of automated pupillometry compared with manual examinations show consistently lower inter-observer discrepancy and increased agreement in pupillary measurements with the use of automated pupillometry, suggesting that standard practice in pupillary monitoring yields inaccurate data. The evidence supports automated quantitative pupillometry as a more reliable method with which to collect pupillary measurements at the bedside for populations of critically ill patients requiring neuromonitoring [11, 14, 18–21].

Multiple studies provide evidence that automated pupillometry can detect subtle pupillary changes and do so earlier than manual examination [14, 19, 22, 23]. The NPi is a function of specific automated pupillometers manufactured by NeurOptics® that accurately grades a pupil's response to light using a proprietary algorithm based on normalized variables of the PLR including size, latency, constriction velocity, and dilatation velocity. The NPi has been shown to be particularly useful in pupillary monitoring. The study by Shoyombo et al. [23] examined NPi and CV values simultaneously. Interestingly, they found that 30.9% of observations had either one or both eyes showing a normal NPi with slow CV, or abnormal NPi with brisk CV, suggesting that a briskly reactive pupil is insufficient to conclude that the PLR is normal. The authors concluded that practitioners performing manual pupillary examinations might equate brisk CV with a normal examination, and miss subtle changes in the PLR that could be detected by automated pupillometry. Additionally, the CV–NPi relationship has the potential to be an intriguing, noninvasive biomarker of neurological status, thus lending support to the idea that automated pupillometers may allow for a more accurate representation of neurological status and function.

Evidence also supports the ability of automated pupillometers to detect pupillary changes that indicate a rise, or impending rise, in ICP. Increased asymmetry of both pupillary size and dilation velocity appears to be associated with increased ICP [18, 24]. An NPi < 4.15 at the time of ICP measurement in neuroICU patients is also associated with a higher risk of developing ICP crisis [25].

Studies examining the ability of automated pupillometry to detect the level of analgesia and depth of sedation show that pupillometry technology may be useful in determining whether analgesia levels need to be adjusted in critically ill patients that are unable to verbally communicate prior to a noxious procedure [27, 29, 31]. Additionally, data show that automated pupillometry may be more useful in the evaluation of sedation in the ICU when compared to BIS [28]. Wildemeersch et al. [32] showed that automated pupillometry may have utility in evaluating patients' specific analgesic needs, especially in those who are not able to report pain levels themselves.

Numerous studies demonstrate the value of automated pupillometry as a prognostic indicator post-cardiac arrest [24, 33–43]. These studies conclude that quantitative measurement of pupillary light reflexes has prognostic value as early as within 1 h after return of spontaneous circulation [33]. Additionally, they showed that quantitative PLR post-cardiac arrest may equal the prognostic value of electroencephalography and somatosensory evoked potentials for poor outcomes [34–36, 38, 39, 41] and predict favorable outcome if PLR is detected during resuscitation [37, 42]. Park et al. [44] also looked at prognosis in acute brain injury and found that initial NPi value had good sensitivity and specificity in predicting clinical outcome at 1 month after injury. Furthermore, Natzeder et al. [26] demonstrated that there is a statistically significant association between the frequency of pathological NPi values and poor clinical outcome in patients with aSAH. This same study provided evidence that NPi reflects the clinical severity of aSAH and may be useful to estimate the clinical severity of other neurological injuries.

Finally, Ong et al. [45] found that NPi values show statistically significant improvement after administration of osmotic therapy in patients admitted to the neuroICU with increased ICP and brain herniation. These results suggest that improvement in pupillary reactivity measured by serial quantitative pupillometry could serve as a noninvasive biomarker for reduction in cerebral edema, intracranial pressure, and/or displacement of midbrain and medullary structures after osmotic therapy.

Secondary Outcomes

Several authors have reported that pupillary signs detected by automated pupillometry have led to changes in therapy. However, no high-quality study has evaluated whether these changes improve clinical outcomes. Although not meeting inclusion criteria for this review, Chen et al. [10] described the case of one patient initially presenting after TBI with an abnormal NPi score of 0.7 for the right pupil, which in the context of a concerning neurological examination, raised questions about impending ICP issues. Repeated NPi measurements over the course of the next 8 h showed improvement in the pupillary function of her right eye. However, over the same monitoring period her pupillary asymmetry did not improve, and a decision had to be made to follow an observational treatment paradigm or pursue neurosurgical invasive techniques. Based off of the improving NPi measurements, the care team decided to decrease sedation, and she subsequently awoke, followed commands, and was extubated according to protocol. This case report suggests that there may be added value to patient care by examining pupils with automated pupillometry technology; however, proof of this added value is difficult to demonstrate.

Potential Limitations of Pupillometry Technology

Potential limitations to the use of objective pupillometers have been raised by several studies. Multiple authors have questioned whether different pathologies may be more or less susceptible to PLR changes [12, 16, 23]. Additionally, Kramer et al. [46] reported a case study wherein a neurologist that observed the pupil for 7–9 s was able to detect a 1-mm size change that was undetectable by pupillometry. They advised that the combined use of the manual examination and automated pupillometry may optimize the accuracy of the assessment of pupillary reactivity. However, the authors proposed that because the light stimulus delivered by the specific pupillometer used in the study lasts only 0.8 s, and subsequent recording of the pupillary constriction occurs for 3.2 s, the relatively brief stimulus and narrow window of recording may miss detection of very slow light reactivity. This can be addressed by changing the parameters of the pupillometer.

Additionally, several authors describe multiple clinical conditions that limit the ability of automated pupillometry to accurately measure pupillary function. These include periorbital edema [14, 47], sporadic movement in the patient with impaired cognition [14], cataract or a prosthetic eye [14], and other facial and ocular injuries that prevent visualization of the pupil [16, 47].

Although it has been claimed that the NPi is less vulnerable to confounding environmental factors such as variable ambient light conditions than standard methods of assessing pupil reactivity, Ong et al. [48] showed that changes in NPi levels under varying light conditions differ significantly in critically ill subjects. Given these findings, the authors recommended that practitioners should standardize lighting conditions to testing in dimly lit conditions in order to maximize measurement reliability and to achieve an optimal assessment of pupillary reactivity.

Financial cost has also been identified as a possible limiting factor to widespread adoption of automated pupillometry technology. Emelifeonwu et al. [12] described the costs involved in purchasing one specific brand of automated pupillometer as approximately $8000 (£5000) for the handheld machine, and $80 (£50) for each single-use detachable headrest, which facilitates placement of the pupillometer device in front of the eye. Regular use of this specific automated pupillometer would have significant cost implications. However, over time the retail cost of pupillometry technology has decreased, and a single unit from a leading commercial brand (NeurOptics®) can currently be purchased for less than $5000 [49].

A study assessing the length of time nurses at a high volume neuroICU spent completing a manual pupil examination showed that, on average, nurses spent 45.8 min per patient per day performing manual hourly pupil examinations and entering the data into the patient's chart [50]. On average, nurses saved 19.8 min per patient per day using an automated pupillometer capable of uploading data directly to the patient's chart [50]. The amount of time saved by use of automated pupillometers only increases with increasing frequency of serial pupillary examinations. This suggests that any improvement in workforce efficiency provided by the use of automated pupillometers may translate into increased productivity and, ultimately, cost-saving benefits. Further research is needed to explore the cost implications of automated pupillometry technology in the neuroICU.

Study Limitations and Recommendations

With this systematic review, we set out to examine whether sufficient evidence now exists to validate routine use of automated quantitative pupillometry in the care of critically ill patients in the neuroICU. In considering the evidence in support of our primary outcomes, every study had a study grade of low to very low according to GRADE criteria. Although an increasing number of studies continue to show that automated pupillometry could have value in assessing our primary outcomes, the low grade of the reviewed studies calls this into question. Automated pupillometry should be considered for use in all critically ill patients with neurological impairment, but at this time there is insufficient high-quality evidence from randomized controlled trials and careful observational studies to strongly recommend routine use of pupillometry technology.

Another limitation of our study is that we only reviewed publications in English, limiting generalizability. Our eligibility criteria may also have caused us to exclude studies examining outcomes in healthy and non-neurological critically ill patients that could be applicable to the neuroICU patient population. Additionally, a major limitation of our study is that baseline pupillometry values for populations in the neurocritical care setting have not been published, which limits application of the technology. However, the increasing use of registries, such as the Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care Registry, provides a large data set of pupillary size, reactivity, and speed of contraction in a cohort of patients admitted to a neuroscience ICU with a variety of conditions. These registries are helping to establish normative data for pupillometer readings for neurologically impaired patients [51].

Conclusion

This extensive literature review has aimed to explore the current state of automated pupillometry technology and its application in the neuroICU. At present, no consensus guidelines exist endorsing routine use of automated pupillometry in this setting. However, an increasing quantity of research supports the usefulness of automated pupillometry to: increase precision, reliability, and reproducibility compared with the manual pupillary examination; detect subtle and early pupillary changes; detect pupillary changes that indicate a rise, or impending rise, in ICP; detect level of analgesia and depth of sedation; serve as a prognostic indicator; estimate the clinical severity of aSAH; and serve as a non-invasive monitor of response to osmotic therapy. Yet, limitations of the current technology are evident and provide direction for future research and development. Additional large-scale prospective studies and randomized controlled trials evaluating the capabilities of automated pupillometry technology and the practicality and cost implications of its routine use in the neuroICU are needed before updated consensus guidelines recommending wider adoption are produced.

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Authors' Contribution

SSP and CMM provided substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data.

RGN and YMK provided substantial contributions to the analysis and interpretation of data for the work. SSP and CMM drafted and critically revised the work for important intellectual content. RGN and YMK critically revised the work for important intellectual content. SSP, CMM, RGN, and YMK provided final approval of the version to be published. SSP, CMM, RGN, and YMK agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with Ethical Standards

Conflict of interest
Raul G. Nogueira declares that he has no conflict of interest related to the topic or work under consideration. Other unrelated disclosures include Stryker Neurovascular (DAWN Trial Principal Investigator—no compensation, TREVO Registry Steering Committee—no compensation, Trevo-2 Trial Principal Investigator—modest; Consultant—modest); Medtronic (SWIFT Trial Steering Committee—modest; SWIFT-Prime Trial Steering Committee—no compensation; STAR Trial Angiographic Core Lab—significant); Penumbra (3D Separator Trial Executive Committee—no compensation); Cerenovus/Neuravi (ENDOLOW Trial Principal Investigator, ARISE-2 trial Steering Committee—no compensation, Physician Advisory Board, modest); Phenox (Physician Advisory Board, modest); Anaconda (Physician Advisory Board, modest); Genentech (Physician Advisory Board—modest); Biogen (Physician Advisory Board—modest); Prolong Pharmaceuticals (Physician Advisory Board—modest); and Allm Inc. (Physician Advisory Board—no compensation). Editor-In-Chief Interventional Neurology Journal (no compensation) and remaining authors declare that they have no conflict of interest.

Human and Animal Rights
This article does not contain any studies with human participants or animals performed by any of the authors.

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