2022

Association between Neurological Pupillary Index and Constriction Velocity in Traumatic Brain Injury Patients and Discharge Disposition: A Retrospective Project

Sunita Khadka

Association between Neurological Pupillary Index and Constriction Velocity in Traumatic Brain Injury Patients and Discharge Disposition: A Retrospective Project

Sunita Khadka

A DNP Project submitted in partial fulfillment

of the requirements for the degree of

Doctor of Nursing Practice

Seattle University

June 2022

Approved by: Diane K Fuller Switzer Date: June 1, 2022
DNP Project Faculty Mentor:
Diane Fuller Switzer DNP, ARNP, RN, FNP-BC, ENP-BC, ENP-C, FAEN, FAANP

Approved by: Benjamin J Miller Date: June 1, 2022
DNP Project Reader: Benjamin J Miller, Ph.D., ARNP, FNP-C, ACNPC, ENP-C FAANP

Acknowledgments

First, I would like to thank Seattle University faculty mentors: Prof. Diane Fuller Switzer and Benjamin J Miller, for their mentorship and continued support throughout the development of this scholarly project. To Prof. Diane Switzer, thank you for your enthusiasm, support, and guidance since the beginning of this project. Prof. Ben Miller, thank you for challenging, encouraging, and giving insightful comments and feedback to ensure this scholarly project's optimum quality. I want to extend my gratitude to both of you.

Second, I would like to thank my project site mentors, Dr. Abhijit Lele and Pat Blissitt. To Dr. Lele, I am incredibly grateful for your excitement, guidance, and support. To Pat, thank you for listening and brainstorming with me in finding the topic for the scholarly project. I hope the findings from this project will help close the practice gaps and barriers in implementing routine usage of an Automated pupilometer in the unit.

Lastly, I would like to thank my husband, Jeff, and my son, Sean, my family, and friends for providing emotional support and continuous encouragement throughout my years of study and throughout this scholarly project.

Abstract

Background: Autonomic pupillary dysfunction and neurological deterioration are common after both primary and secondary traumatic brain injury and require frequent pupillary and neurological assessment. An automated pupillometer has provided promising results in predicting pupillary changes and patient outcomes in Traumatic brain injury. **Aim:** This project aimed to explore the prevalence of automated pupillometer in the neurosurgical intensive care unit. This project hypothesized that there is no association between Neurological pupil index, constriction velocity, and discharge disposition. **Methods:** Automated pupillary assessment using an automated pupillometer (NPi-200) was performed on patients with traumatic brain injury between January 2014 and January 2022. **Results:** In this retrospective study, 8,034 quantitative pupillary assessments were performed (n=618; mean age= male 51 years, female 61 years, males, 72%). 307 (49.7%) had unfavorable outcomes among the included patients, with 230 (74.9 %) expired. Initial NPi ($p < 0.001$), initial CV ($p = 0.005$), mean NPi ($p <0.001$), and mean CV ($p <0.001$) were noted among TBI patients with favorable outcome. Age was independently associated with discharge disposition (adjusted OR 0.94, 95% CI 0.93-0.95, $p <0.001$). **Conclusion:** Serial pupillary assessment by an automated pupillometer could help provide a rapid and precise measurement in traumatic brain injury patients. There is a strong relationship between the lowest initial and mean NPi and CV and discharge disposition.

Keywords: Traumatic Brain Injury, Pupillary light reflex, Automated pupillometer, Neurological pupil index, Constriction Velocity, Increased intracranial pressure, Neurosurgical intensive care unit

Table of Contents

Association between Neurological Pupillary Index and Constriction Velocity in Traumatic Brain Injury Patients and Discharge Disposition: A Retrospective Project

Traumatic brain injury (TBI) is an acute and chronic disease associated with trauma-induced neurodegeneration and long-term cognitive deficits such as impaired memory, impaired executive function, and emotional instability (Xiong et al., 2018). It is a major cause of death and disability in the United States, with significant disparities in access to care, especially in non-urban settings (Anderson et al., 2019). In addition, the initial injury, also known as primary injury, is often associated with secondary injuries, such as tissue hypoxia, seizures, or cerebral edema, which further complicates the recovery process with the development of intracranial hypertension (ICH) and cerebral herniation (Ma et al., 2016). Therefore, TBI management focuses on preventing and treating secondary brain injury and intracranial pressure control following the primary cerebral insult.

Performing a thorough neurological examination is the most critical process while caring for patients with brain injury. A vital part of neurological examination is to assess cranial nerve function. The non-invasive pupillary exam is an integral part of TBI patients' neurological assessments in the Neurosurgical Intensive Care Unit (NICU), as the aftermath of both primary and secondary injury may alter brainstem function and cause abnormalities in pupil size, symmetry, and pupillary light reactivity (Lee et al., 2018; Xiong et al., 2018). In addition, unlike other components of the neurologic examination that require patients to be conscious, the pupillary examination is one of the few neurologic signs that can be assessed in an unconscious patient or a patient receiving neuromuscular blocking agents and sedation (Zakaria et al., 2020).

The standard pupil examination most commonly involves visual assessment of pupil size, shape, symmetry, and pupillary light reflex as it assesses the function of cranial nerves II and III

and is used as a rapid assessment for increased intracranial pressure signifying a worsening TBI and need for emergent intervention (McNett et al., 2018). The current standard practice is using a penlight to observe the pupillary light reflex (PLR). However, the accuracy of PLR is confounded by the subjective nature of inter-examiners variability and inter-reliability. For example, Olson et al. (2015) found that "when using a manual penlight, the median absolute error rate in pupillary size measurements was more than twice the size of the median total error rate in pupillary size measurements made with an automated pupillometer" (p. 2). These findings have been constant and replicated in multiple settings using various research methods (Couret et al., 2016; Kerr et al., 2017).

Despite several studies showing the superiority of automated pupillometer (AP) and its emerging as a mainstay tool in NICU (Couret, 2016; Olson, 2013; Taylor, 2003), there is still a lack of standardization on utilizing the AP policies protocol and varied consensus among the providers in NICU (see Figure 1.1 for AP policies). In addition, the usage of a pupillometer in the Neuro Intensive Care Unit (NICU) has always been dependent on order from the Neurosurgery team when patients are admitted with Traumatic Brain Injury (TBI) with no defined detailed instruction on the frequency, duration, and severity class of patient population to perform. Thus, a lack of standardized performance and utilization might not help detect neurological decompensation early on.

There are studies done that focused on the correlation between Neurological Pupil Index (NPi) and intracranial pressure (Jahns et al., 2019), NPi and Transtentorial herniation (Papangelou et al., 2018), and NPi with Transcranial Doppler (TCD) and delayed cerebral ischemia (DCI) (Aoun et al., 2020). Most of these studies in small sample sizes have shown the importance of abnormal NPi in conjunction with other modalities such as imaging, external ventricular drain, and

transcranial doppler in guiding and managing these patients. However, few studies have assessed and established the predictive values of the AP parameters in conjunction with different intracranial pathologies and clinical outcomes. Automated pupillometry has been gaining traction as an evidence-based tool to eliminate the risk of subjective interpretation of pupils and has provided the objective, precise measurement of PLR (Aoun et al., 2020; El Ahmadieh et al., 2021; Emeilfeonwu et al., 2018; Zafar et al., 2014). However, there is a need to investigate further the full potential of AP variables to utilize as a standard assessment tool in NICU to improve patient outcomes.

The main aims of this project were to 1) describe the prevalent patterns of using pupillometer in neurocritical care, 2) examine the existing association between the initial NPi and the discharge disposition, 2) explore the association between the initial CV and the discharge disposition, 3) investigate whether the mean NPi/CV is associated with the discharge disposition, and 4) identify whether there is a relationship between NPi and CV.

Background and Significance

Epidemiology of TBI

Known as the "silent epidemic," an estimated 69.0 million people worldwide suffer from TBI each year (Haarbauer-Krupa et al., 2021). The low-income countries experience the highest disease burden, mostly from motor vehicle accidents (Dewan et al., 2018). In a recent surveillance report, the Centers for Disease Control and Prevention (CDC, 2022) reported that in 2018, suicide accounted for 35.5% of the reported TBI-related death, firearms-related suicide accounted for 48.3%, 29.9% for unintentional falls, and 17% for motor vehicle accidents.

American Indian/Alaska Native children have the highest TBI-related deaths compared to other races and ethnicities, with motor vehicle accidents, substance use, suicide, and disparities in healthcare access being the significant contributors, followed by African American and Hispanic children (Simon, 2022; Maas et al., 2017). Older adults aged seventy-five and older average the highest annual TBI rate among suicide and fall, followed by young adults aged 15-24 years and young children aged 0-4 years from homicide and unintentional motor vehicle accidents (CDC, 2022). The overall leading causes of TBI in the United States are motor vehicle-related injuries, falls, and assaults (Naseri Alavi et al., 2018), with males leading three times higher than females (Capizzi et al., 2020).

The CDC estimated that between 3.2 and 5.3 million persons in the United States live with a TBI-related disability, including several neurocognitive disorders and functional limitations (Sulhan et al., 2018). At an individual level, neurological deficits, behavioral alterations, and cognitive decline following TBI are often common resulting in reduced quality of life. At the societal level, it has become a significant public health problem due to the loss of the workforce, the burden on healthcare systems, and the impact on environmental issues such as family burden,

social participation, and health inequities (Haarbauer-Krupa et al., 2021; Khellaf et al., 2019). In addition, the lifetime economic cost of TBI, including direct and indirect medical costs, was estimated to be $76.5 billion in 2010 dollars (CDC, 2019).

Physiology of Brain

The brain is the largest and most complex organ in the body, encased inside the skull, suspended in the cerebrospinal fluid (CSF), and isolated from the bloodstream by the blood-brain barrier (see Figure 2.1). The CSF is an ultrafiltrate of plasma produced by the choroid plexus, approximately 20 ml per hour; it assists the brain by providing nourishment, waste removal, and protection to the brain (Telano & Baker, 2021). The brain is covered by the three layers (dura mater, arachnoid mater, and pia mater) of protective covering called meninges and divided into the cerebrum, the cerebellum, and the brainstem. The cerebrum accounts for 83% of the total brain mass and divides into left and right hemispheres, containing frontal, parietal, temporal, and occipital lobes. It is responsible for processing information associated with movement, smell, sensory perception, language, communication, memory, and learning. In addition, the cerebellum coordinates skeletal muscle contractions, regulates balance and posture, and may have a role in language processing and cognition (Standring, 2012).

The brainstem gives rise to cranial nerves III through XII, whereas cranial nerves I and II arise from the cerebrum. It provides the primary motor and sensory innervation to the face and neck and is further divided into the midbrain, pons, and medulla oblongata. The midbrain is associated with vision, hearing, motor control, sleep and wake cycles, alertness, and temperature regulation. The pons lies between the medulla oblongata and the midbrain. It contains tracts that carry signals from the cerebrum to the medulla and the cerebellum and relays sensory signals to

the thalamus. The medulla oblongata contains the cardiac, respiratory, vomiting, and vasomotor centers that regulate heart rate, breathing, and blood pressure.

The central nervous system comprises the brain and the spinal cord. It is the central control network for the body's functions and abilities, enabling conscious communication with the body and automatic operation of vital organs, such as the heart (Maldonado & Alsayouri, 2021). Hadanny & Efrati (2015) stated that "the brain comprises only about 2 % of the body's total weight but uses about 15 % of total cardiac output, 20 % of total oxygen supply, 25–30 % of total body glucose consumption, and 30 % of total body energy consumption" (p. 2).

Monro-Kellie Doctrine

Known as the Monro-Kellie doctrine, hypothesized in 1783 A.D, it describes that the brain tissue, blood, and cerebrospinal fluid (CSF) inside the cranial vault in a normal state, autoregulate to maintain a normal intracranial pressure (Kalisvaart et al., 2020). This equilibrium between these three components is vital to maintain a continuous cerebral perfusion pressure (force driving blood into the brain, providing oxygen and nutrients) and intracranial pressure (pressure exerted by cranial contents and indicator of intracranial compliance) (Kenosita, 2016).

The cerebral perfusion pressure (CPP) is the primary determinant of cerebral blood flow (CBF) and is dependent on the intracranial pressure (ICP) and mean arterial pressure (MAP), and its normal range is 60 to 80 millimeters of mercury (mm Hg). The normal range of ICP is 5-15 mm Hg and is considered abnormal if it is greater than 20 mm Hg for five minutes or more (Martini et al., 2022). When the ICP increases beyond the limit of auto compensatory mechanisms, cerebral perfusion can be compromised, and brain tissue ischemia may occur (Chestnut et al., 1993; Stocchetti et al., 2017). Studies have shown that mortality can be significantly reduced in TBI patients when CPP is maintained above CPP above 70 mm of Hg (Dash & Chavali, 2018).

Classification of TBI

Traumatic brain injury is a colossal multiplex heterogeneous condition involving the body's most complex organ. Broad variations in the clinical presentations, patterns, and extent of damage to TBI are attributed to the complexity of the brain and the type, intensity, direction, and duration of the external forces. Therefore, understanding and classifying the pathophysiology after TBI is paramount for acute management, treatment, prognosis, neurorehabilitation requirements, and prevention of secondary injuries (Kinoshita, 2016).

TBI is categorized according to etiology, pathophysiology, and severity, as assessed by neuroimaging and physiological responses. TBI has four mechanical causes: direct impact, acceleration and deceleration, penetrating injury, and blunt injury (Capizzi et al., 2020). The pathological injuries caused by these different mechanisms of mechanical forces are classified as focal or diffuse based on the presence or absence of focal lesions; primary and secondary based on the direct or indirect results from the trauma (McKee & Daneshwor, 2015), and mild, moderate, and severe TBI depending on the degrees of severity (Brennan et al., 2018).

Classification by Physical Mechanism

The etiological classification of head injuries by physical mechanism of injury has certain advantages in understanding how specific forces at specific magnitudes result in predictable patterns of injury (Saatman et al., 2008). TBIs occur from contact or direct injury to the head (the head is struck or strikes an object) and from acceleration-deceleration injury (the brain moves within the skull from non-contact or inertial loading) (Fakharian et al., 2018). The immediate impact of different primary mechanical insults to the brain can cause focal and diffuse brain injuries depending on patterns of tissue damage. Even though there are differences in clinical manifestation between focal and diffuse injury, Vos (2011) found that "Pure forms of focal injury

occur in 28% of moderate/severe TBI cases, pure diffuse axonal injury in 22%, while mixed focal and diffuse injuries occur in 50%" (p. 2).

Focal Injury. Produced by collision forces acting on the skull and resulting in tissue compression underneath the cranium or of tissue oppositely to the impact. The location and severity of impact to the skull determine the cerebral pathology and neurological deficits. It usually occurs due to contact forces causing contusion, laceration, skull fractures, and intracranial hemorrhage, which are detectable in computer tomography (CT) and magnetic resonance imaging (MRI) scans. Depending on the severity of the injury, it can lead to cognitive deficits, behavioral changes, and hemiparesis (Ng & Lee, 2019).

Contusion and Laceration. Focal contusions are bruises or swelling in a small, specific area of the brain, most often the inferior aspect of the frontal lobes and the inferior aspect of the temporal lobes. They are often called "coup," a bruise directly on the impact site, and "contra-coup," a bruise on opposite sides or both sides of impact. A laceration occurs due to physical disruption of the brain parenchyma and may occur in combination with contusions along the surface of the brain (McKee & Daneshvar, 2015).

Skull Fractures. Indicates considerable mechanical forces to sustain skull fractures. The location and severity of impact on the skull determine the cerebral pathology and neurological deficits. They are significantly more likely to have subarachnoid, subdural, or epidural hemorrhage. Fractures of the base of the skull often involve the middle ear or anterior cranial fossa with leakage of spinal fluid from the ear (otorrhea) or nose (rhinorrhea) and cranial nerve damage (Ng & Lee, 2019).

Hemorrhage or Hematoma. Bleeding inside the skull or the brain is the most common cause of death and clinical deterioration after TBI. It encompasses four broad types of intracranial

and extracranial hemorrhage: epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, and intraparenchymal hemorrhage (Capizzi et al., 2020). Each type of hemorrhage has a different etiology, findings, prognosis, treatment, and management. In addition, the patient's outcome depends on the type and extent of bleeding, age, other comorbidities, and severity of neurological deficit at admission (Goldberg & Glazer, 2020).

Epidural hematoma is a medical emergency as bleeding between the dura and skull, often due to injury to the middle meningeal artery, leads to a sudden rise in intracranial pressure after lucidity (Algattas & Huang, 2013). Subdural hematoma accumulates blood under the dura mater but is external to the brain and arachnoid membrane and classically associated with damage to bridging veins. The elderly are at increased risk of chronic subdural hematoma because of their increased risk of falls and greater intracranial space caused by cerebral atrophy (Kaur & Sharma, 2018). Subarachnoid hemorrhage is bleeding into the subarachnoid space and is the most common form of vascular injury after head trauma. It results in communicating type of hydrocephalus or the non-communicating type of hydrocephalus, inferior to the blood clot blocking the third or fourth ventricles (Sulhan et al., 2018). Intraparenchymal hemorrhage is bleeding within the brain; it primarily occurs inside the cerebral parenchyma inferior to lacerations or brain contusion (Kaur & Sharma, 2018).

Diffuse Injury. Produce more consistent effects and entail widely distributed damage to axons, diffuse vascular injury, hypoxic-ischemic injury, and cerebral edema (Andriessen et al., 2010). Rapid and sudden acceleration-deceleration of the head from motor vehicle accidents is responsible for the diffuse injury, causing shearing, stretching, and twisting of the brain tissue (Abu Hamdeh et al., 2018). In addition, the degree of axonal injury and neuronal degeneration determines the severity of TBI (Saatman et al., 2008).

Diffuse Axonal Injury (DAI). Ma et al. (2016) explained that "DAI is a brain injury characterized as axonal injury of the white matter, which often follows brain trauma and causes wide-ranging denaturation of white matter, focal hemorrhage, and the emergence of axonal retraction balls, and microglia clusters" (p. 1). It occurs in half of the severe head traumas and often causes a persistent vegetative state (six hours or more) and is a significant cause of morbidity among TBI patients, and can increase the risk of neurodegeneration, including Alzheimer's disease-like pathology (Davceva et al., 2017; Galgano et al., 2017).

Classification by Pathophysiological Mechanism

Primary Injury. It is a non-reversible injury from the focal (intracranial hematomas, skull fractures, lacerations, contusions, and penetrating wounds) and diffuse mechanical insults imposed on the brain during the insult (Kaur & Sharma, 2018). It results in tissue deformation, necrosis, and shearing of neurons, axons, and glial cells, causing tissue destruction and distortion (Jassam et al., 2017; Maas et al., 2017; Xiong et al., 2013). As illustrated in Figure 2.2, these forces deregulate CBF and cause direct cellular injury, which leads to excitotoxic neuronal death instigating the reduced CBF to deregulate cerebral metabolism and deplete energy stores within the brain (Algattas & Huang, 2013).

The physiologic injuries cause pathologic breakdown in the blood-brain barrier (BBB), a multicellular vascular structure that acts as a diffusion barrier from bacteria, viruses, and the influx of unwanted xenobiotics and maintains the homeostasis between blood circulation and the CNS (Shetty et al., 2014). Deterioration in BBB function may play a significant role in disease pathogenesis since the BBB dynamically responds to many events associated with flow disturbances, free radical release, and cytokine generation (Kadry et al., 2020). In addition, this

disruption can lead to decreased cerebral perfusion pressure and systemic changes in cerebral blood flow (hypo and hyperperfusion) (Alluri et al., 2015).

Secondary Injury. The primary, irreversible tissue damage at impact results in immediate necrotic cell death and initiation of a cascade of secondary brain injury (see Figure 2.2). It is a leading cause of in-hospital deaths after TBI and is primarily responsible for development of delayed intracranial hypertension (McKee & Daneshvar, 2015). A physiologic response consists of a molecular, chemical, and inflammatory cascade responsible for further cerebral damage due to cerebral ischemia, anatomical distortion, and compression of the brain or mass effect (Galgano et al., 2017; Ponsford et al., 2012). Ladak et al. (2019) summarized secondary injury:

> Excitotoxicity, neuroinflammation and cytokine damage, oxidative damage, and eventual cell death are prominent mechanisms of cell damage post-TBI. Excitotoxicity primarily results from upregulated glutamate receptors in a glutaminergic storm, leading to overexcited cells. Neuroinflammation is induced by microglial cells in the brain that damage the BBB to increase the levels of cytokines, complement proteins, and other inflammatory mediators within the brain parenchyma. Neuroinflammation also leads to the accumulation of reactive oxygen species that causes lipid peroxidation, protein carbonylation, and DNA oxidation, leading to membrane permeability and fluidity changes. Finally, through increased membrane permeability, caspases are activated, causing apoptosis, and necrosis and autophagic mechanisms also cause cell death. The molecular mechanisms highlighted here give way to the long-term sequelae of TBI like epilepsy, Alzheimer's disease, Parkinson's disease, and chronic traumatic encephalopathy due to impaired electrical circuitry and oxidative imbalance (p. 130).

Hypoxemia and hypotension occur commonly in the pre-hospital setting and significantly increase the risk of secondary brain injury and the likelihood of a poor outcome (Kinosita, 2016). Studies done by Ng & Lee (2019) and Patel and Sabini (2021) concluded that the prognostication factors such as age, pupillary reaction, and Glasgow coma scale of primary brain injury could determine the prediction of the outcome.

Measure of Severity

Understanding the severity of TBI helps with the prognosis of functional recovery and anticipating patients' rehabilitation needs (Capizzi et al., 2020). The clinical severity of TBI can be quantified using three different measurement tools as described below.

Glasgow coma scale (GCS). In 1976, Graham Teasdale and Bryan J. Jennett developed the scaling tool to assess and monitor a patient's level of consciousness or responsiveness and determine the severity of TBI ("Glasgow Coma Scale," 2015). The scoring is based on the best eye-opening response (1-4 points), best motor response (1-6 points), and best verbal responses (1-5 points). Then, the severity of TBI is graded based on total score: mild TBI (mTBI) with a score of 13-15, moderate TBI (modTBI) with a score of 9-12, and severe TBI (sTBI) with a score of 3-8 (see Figure 2.3).

Of all severities of TBI, an estimated 75–85% are categorized as mTBI, in most cases, caused by a concussion, and there is full neurological recovery, although many of these patients have short-term memory and concentration difficulties (Capizzi et al., 2020; McKee & Daneshvar, 2015). Remaining approximately 20% of TBI patients are with 10% modTBI and 10% sTBI, with the incidence of modTBI is about 15 cases per 100,000 people, and 14 cases per 100,000 people for sTBI (Abdelmalik et al., 2019). The median hospitalization cost for mod/sTBI is $55,267 per case, and it is estimated that there are 5.5 million cases of mod/sTBI (Dewan et al., 2019). Studies

have shown that initial GCS scores are associated with outcomes, and a lower GCS score is associated with a worse outcome (Majdan et al., 2017). Although GCS is an objective measurement, it can be confounded by interrater differences, use of paralytics for agitation, intubation, or alcohol and drug intoxication (Brennan et al., 2018).

Duration of Loss of Consciousness (LOC). Roy et al. (2020) concluded that the occurrence of LOC or altered LOC at the time of injury must be viewed as a potential worrisome traumatic brain injury. As shown in Figure 2.4, the LOC is classified as mild (mental status change or LOC for less than 30 min), moderate (mental status change or LOC for 30 min to 6 hr), or severe (mental status change or LOC >6 hr) (Hawryluk & Manley, 2015).

Duration of Post-Traumatic Amnesia (PTA). The PTA is the time elapsed from injury to the moment when patients can demonstrate continuous memory of what is happening around them ("The Epidemiology and Pathophysiology of Traumatic Brain Injury," 2021). The PTA of less than 24 hours is classified as mild, 1-7 days moderate, and more than seven days severe (see Figure 2.4). A study done by Hart et al. found that despite GCS of 13-15, the patients with PTA lasting longer than one week showed moderate residual disability at the 6-month assessment (2016).

Pupillary Light Reflex

The pupil is controlled by the two divisions of the autonomic nervous system, and its reflexes are controlled by the activation of two sets of antagonistic muscles embedded within the iris stroma (Larson & Behrends, 2015). The normal pupil size in adults varies from 2 mm to 4 mm in diameter in bright light to 4 mm to 8 mm in the dark and is equal in size. The pupillary light reflex is an autonomic reflex that constricts the pupil in response to light, thereby adjusting the amount of light that reaches the retina. Pupillary constriction occurs via innervation of the iris

sphincter muscle, controlled by the parasympathetic system. In addition, PLR requires cranial nerve II (Optic nerve), III (oculomotor), and central brain stem connections (Adoni & McNett, 2007; Lynch, 2018).

When light is shined in one eye, it results in the constriction of both pupils (ipsilateral pupillary constriction-direct response; contralateral pupillary constriction-consensual response) (Yoo & Mihaila, 2021). First, it stimulates retinal photoreceptors and retinal ganglion cells, whose axons travel through the optic nerve, chiasm, and tract to terminate in the pretectum (pretectal nucleus) (Belliveau et al., 2021). Second, the pretectal neurons project to a portion of the nucleus of Edinger-Westphal (E-W) of the oculomotor complex on both sides. Third, the efferent pupillary parasympathetic preganglionic fibers travel on the oculomotor nerve to synapse in the ciliary ganglion from the E-W nucleus. Finally, it sends parasympathetic postganglionic axons in the short ciliary nerve to innervate the iris sphincter smooth muscle via M3 muscarinic receptors (see Figure 2.5).

The complexity and variability of the PLR are introduced by the contraction strength of the antagonistic radial muscle and the impact of a variety of circulating hormones, medications, and pathophysiological changes on the functionality of the active neurons and muscles (Boulter et al., 2021). Injury anywhere along its route can result in abnormal static (i.e., steady-state or baseline) and dynamic (transient) pupillary responsivity (Ciuffreda et al., 2017). For example, pupils can become mydriatic, or dilate, in response to potential disease, drug toxicity, trauma, increased intracranial pressure, brainstem damage, or nerve damage to cranial nerves II and III (Lynch, 2018). In addition, bilateral ipsilateral monocular vision loss can occur if the injury is before the optic chiasm (Belliveau et al., 2021). Similarly, downstream to the optic chiasm, damage to the optic tract will produce contralateral homonymous hemianopia; uncal herniation, in which the

uncus protrudes over the edge of the tentorium, can lead to compression of CN III, suggesting current or impending brainstem compromise (Yoo & Mihaila, 2021).

The optic nerve carries sensory nerve impulses from the more than one million ganglion cells of the retina toward the visual centers in the brain and is located on the diencephalon. The oculomotor nerve innervates most extraocular muscles (levator palpebrae superioris, superior rectus, inferior rectus, medial rectus, and inferior oblique). It is in the midbrain of the brainstem, ventral to the cerebral adequact (Belliveau et al., 2021). As they are located superior to other cranial nerves, they are extremely sensitive to any subtle changes, and their dysfunction can indicate more serious underlying processes.

The pupillary function provides information on any sustained or new-onset pupillary abnormalities associated with a worse outcome (Jhans et al., 2019). For example, the study done by Brennan et al. (2018) concluded that "the frequency of loss of pupil reactivity increased with TBI severity: 2.1% in mild TBI, 5.5% in moderate TBI, and 35.7% in severe TBI" (p. 3). Additionally, the combination of the pupillary examination and GCS score provides more accurate prognostic information, and patients with a GCS of 3 with reactive pupils have a 33% survival rate, as opposed to patients with a GCS of 3 and fixed dilated pupils who have no reasonable chance of recovery (Lieberman et al., 2003).

Automated Pupillometer

According to NeurOptics (2021), the Neurological pupillary Index (NPi)-200 automated infrared pupillometry is a non-invasive handheld device that uses an infrared camera that integrates a calibrated light stimulation to provide a rapid measurement of pupil size and quantitative PLR (i.e. the difference between baseline and post-stimulation pupil size, expressed as % of constriction from the baseline value), constriction velocity and latency (see Figure 2.6). The measurement is

completed in less than 30 s for each eye. In addition, a minimum duration of one minute was allowed between appraisals of the two pupils to obtain full recovery of baseline pupil diameter after light stimulation.

The AP digitally calculates and displays NPi numeric results on a display screen based on the integrated algorithm. The NPi incorporates maximum/minimum size, contraction amplitude, constriction velocity (CV), mean CV, latency, and dilation velocity (see Figure 2.7). Its values range from 0-5, with zero indicating non-reaction or fixed reaction, less than 3 indicating an abnormal or sluggish reaction, and greater than three indicating normal or brisk reaction (NeurOptics, 2021). NPi is considered abnormal when the NPi difference between pupils is greater than or equal to 0.7 and can be abnormal in one or both pupils (Papangelou et al., 2018).

Constriction is measured in millimeters per second (mm/s) and reported or analyzed as CV, known as a maximum CV. The maximum CV is seen during initial constriction, and the velocity diminishes as the minimum pupillary diameter is reached. The pupil quickly partially constricts before returning to its initial size (Lussier et al., 2019). The CV > 0.8 mm/sec is considered normal, less than 0.8 mm/s suggestive of increases in brain volume, and less than 0.6 mm/s suggestive of ICP elevation > 20 mm Hg or will be elevated within 15-30 minutes (Anderson et al., 2018).

Traditional assessment of the PLR is dependent on clinician assessment skills and light source (intensity and duration) and determining the size, shape, and reactivity of pupils can be difficult due to eye color, patient compliance, and ambient lighting. In contrast, an automated pupillometer benefits from a high-speed camera and computing technology. It can offer a potential solution to the subjective pupillary assessment of critically ill traumatic brain injury patients (Larson & Behrands, 2015). Over the last decade, there has been ongoing studies to evaluate the

acceptability, feasibility, and predictability of automated pupillometry in patients with acquired brain injury.

Organizational Policies and "Gaps" in Practices of Project Site. The large urban regional medical center has a 30-bed NICU divided into three pods and has 5 AP devices; 2 in A-pod, 2 in B-pod, and 1 in AP device located in C-pod. Figure 1.1 describes the AP policy as an adjunct and does not replace traditional manual penlight or flashlight pupillary assessment. The policy recommends the usage of AP on patients with severe TBI (GCS less than 8), unstable intracranial dynamics (increased ICP, decreased CPP, and low brain oxygen tissue), severe cerebral vasospasm, dark eyes, and continuous sedation or drug-induced coma. The policy states that the frequency of pupillometer measurement may vary depending on the patient's condition and clinical judgment.

While there is a power plan on "Automated Pupillometer" on Epic electronic health record system charting, it is an independent "order set." Therefore, it cannot automatically incorporate the patients' order sets that meet the criteria to have frequent AP assessments. In NICU, the providers can choose standardized order sets according to different neurological disease processes, such as TBI order sets, Ischemic stroke order sets, and Subarachnoid Hemorrhage order sets. However, the AP order set is not a component of TBI order sets. Therefore, it must be additionally ordered if the provider wants an AP assessment done, leading to a lack of standardized practices and utilization of AP among the providers and bedside nurses.

Review of Literature

The routine pupillary exam is an integral part of the neurological assessment in the NICU. The main component of the pupillary exam consists of measuring pupillary light reflex, which can be very subtle to naked eyes. Early studies such as Taylor et al. (2003) and Meeker et al. (2005) found more errors with the manual pupillary assessment as the pupil diameter increased. In contrast, Hults et al. (2006) reported that the visual examination was less accurate as pupil diameter decreased. Evaluation of the pupillary light reflex provides information about the functionality of the optic and oculomotor nerves and can indicate the degree of neurological injury, increase in intracranial pressure, and presence of herniation (Mazhar et al., 2021; Shehabeldin et al., 2017, Jahns et al., 2019). In addition, an automated pupillometer has been shown to have superior inter-device reliability and producibility, whereas a manual pupillary observation has been shown to have low interrater reliability and validity (Anderson et al., 2018; Olson et al., 2015).

Any abnormal pupillary dysfunction is a huge concern for potential impending intracranial insults and often warrants further investigation to help minimize secondary insults to the brain. For example, an earlier study by Chestnut et al. (1993) indicated that secondary insults such as hypotension and hypoxia are independently associated with significant increases in morbidity and mortality from severe head injury with hypotension was profoundly detrimental, occurring in 34.6% of these patients and associated with a 150% increase in mortality. In addition, the study conducted by McNett et al. (2017) has shown a correlation between NPi and intracranial pressure resulting from intracranial hypertension(ICHT) and recommended serial trend pupils using AP as an adjunct to the traditional invasive neuromonitoring.

Similar studies by Jahns et al. (2019) and Emeilfeonwu et al. (2018) found that the abnormal NPi values were more frequent in patients with ICHT and were associated with an

unfavorable 6-month outcome. They also found that treatment of elevated ICP with hyperosmolar agents (mannitol or hypertonic saline boluses) was associated with a normalization of the NPi; however, failure of NPi to return to standard value was associated with an abysmal prognosis. In another study conducted by Singer et al. (2021), recovery of NPi was observed within two hours in TBI patients treated with osmotic therapy if the pre-intervention NPi was below 3.

A recent study by Teixeira et al. (2021) examined the prognostic role of the worst NPi in predicting unfavorable neurological outcomes among 100 TBI patients. They found that a lower NPi score on admission was observed in patients with poor neurological outcomes at hospital discharge and high intensity of care for elevated ICP compared to others. However, the prognostic role of AP remained limited and suggested further evaluation in patients with severe TBI.

A prospective study found that changes in AP preceded clinical signs of Transtentorial Herniation (TTH) and may potentially guide the management of critical patients in NICU to improve neurologic outcomes (Papangelou et al., 2018). Despite a small sample size study of 3 TTH patients, this study highlights the importance of using AP in brain tumor patients. In addition, Kim et al. (2020) performed a retrospective chart review on patients with large hemispheric stroke. They concluded that the patients with neurological worsening had a significantly lower mean value of NPi and a sudden decrease in the NPi value than those without neurological worsening during the whole monitoring period. All patients with NPi values below 2.8 showed neurological deterioration.

In contrast, another study found that the clinical benefit of AP appears limited for identifying ICP elevation but reliably determines intracerebral hemorrhage (ICH) in patients without ICP elevation (Giede Jeppe et al., 2020). They further explained that the positive predictive values of all AP parameters ranged less than 10% in isolating ICP elevation and recommended

that non-invasive modalities such as AP and computed tomography are adequate to identify ICH patients without ICP elevation. In addition, AP data failed to differentiate which aneurysmal subarachnoid hemorrhage patients will pass and which will fail EVD weaning (Bezner et al., 2017).

Aneurysmal subarachnoid hemorrhage (aSAH) is caused by extravasated blood in the subarachnoid space due to a ruptured aneurysm. It is often life-threatening, with 25–50% mortality (Weiland et al., 2021). Even though the pathophysiology is not fully understood, initial global hypoperfusion after aSAH leads to inflammatory processes and disruption of blood-brain integrity and other acute processes that contribute to Delayed Cerebral Ischemia (DCI) and poor outcomes. Aoun et al. (2019) reported a significant association between DCI and sonographic vasospasm and between DCI and an abnormal decrease in NPi occurring more than 8 hours before the clinical decline 71.4% of the time. This finding was significant as DCI incidence is greater than 30% and is a significant cause of morbidity and mortality among patients who survive the initial treatment of the ruptured aneurysm (Weiland et al., 2021).

In 2003, one of the earliest AP studies on acute head injury patients compared to healthy volunteers' data suggested significant differences in all AP parameters with the exclusion of latency, with a reduction of CV below 0.6 mm/s on the side of the mass effect (Taylor et al., 2003). Other studies conducted outside the NICU on PLR after the return of spontaneous circulation (ROSC) showed a strong correlation between AP measurement and poor neurologic outcomes and suggested the utilization of AP as an adjunct prognostication tool during resuscitation (Oblong et al., 2019; Tamura et al., 2020).

Only one article was found that studied the relationship between NPi and CV. This study aimed to examine the prevalence of brisk CV in cases with abnormal NPi and paired with GCS in

a NICU setting. Shoyombo et al. (2018) concluded that "the brisk CV does not rule out an abnormal PLR, and the slow CV does not rule in abnormal PLR" (p. 5). This study highlights a lack of research that defines an actual normal value of CV and depends on numerous benign environmental conditions such as ambient light and baseline pupil size. Therefore, a gap in the literature examined this relationship as the expectation that an NPi of less than 3.0 parallels lower CV values is not necessarily a valid assumption.

Methodology

Settings and Participants

This retrospective cohort project was conducted using Epic Electronic Medical Records (EMR) data on patients with traumatic brain injury admitted to NICU between January 1, 2014, and January 31, 2022. The data includes a 30- bed NICU at a large urban medical center, a Level-1 trauma center, and a comprehensive regional stroke center for five state areas. NICU patients with automated pupillometer data were selected from the Epic electronic medical records (EMR) system. Patients (<18 years of age) and any pre-existing ocular damage that could affect pupillary examination were excluded.

Ethical Consideration

This project is identified as "Not Human Participant Research (NHPR)" by Seattle University Institutional Review Board; therefore, the requirement for informed consent was waived. Epic access had been sought and granted by the tertiary academic medical center. Patients' identifiers were removed after getting the data.

Conceptual or Theoretical Framework

The Ottawa Model of Research Use (OMRU), an interactive evidence-based model developed by Logan and Graham (2004) when they became aware of the lack of practical models to promote research use and created a framework that policymakers and researchers could use. The OMRU framework offers a “comprehensive, interdisciplinary framework of elements that affect the process of healthcare knowledge transfer, and is derived from theories of change, from the literature, and a process of reflection” (Graham & Logan, 2004, p. 93).

Patients and their health outcomes focus on knowledge translation processes using evidence-based practice in the OMRU framework. In addition, the OMRU framework supports

healthcare professionals in selecting appropriate strategies and interventions to increase awareness of the innovation and understanding of the innovation and provides skills or training for adopters to conduct the innovation.

The six steps approach of the OMRU framework is considered central to the knowledge transfer, which aligns with the aims and purposes of this project. It includes essential elements: (1) evidence-based innovation, (2) potential adopters, (3) the practice environment, (4) implementation of interventions, (5) adoption of the innovation, (6) outcomes resulting from the implementation of the innovation. The AP was introduced as a new innovative tool a decade ago in the NICU. This retrospective project is conducted to investigate the associated outcome among TBI patients and get an opportunity to pause, reflect, and identify barriers to adopting a new system in the unit. It is essential to highlight that the six key elements are bidirectional. It provides the flexibility to address the sustainability of EBP through organizational culture change, stakeholder engagement, comprehensive literature review and appraisal, barrier identification, impact evaluation, and outcomes dissemination. Figure 3.1 explains how the framework is used as guidance throughout the undertaking of this project.

Data Collection

The automated pupillometer readings were obtained using an NPi-200 automated pupillometry device (NeurOptics, Laguna Hills, California, USA). First, an initial query on the NICU database was conducted to identify patients with TBI. Next, the data were de-identified and exported from the Epic EMR to Microsoft excel. Next, the patients' demographic data (age, sex, ethnicity), NICU and hospital length of stay, initial NPi, lowest NPi, mean NPi, lowest CV, Mean CV, and discharge disposition are extracted from the EMR.

The patients' GCS were grouped into three categories to reflect the severity of brain injury. GCS scores of 3-8 were classified as severe (sTBI), 9-12 as moderate (modTBI), and 13-15 as mild (mTBI) brain injury. Hospital and NICU length of stay data were stratified according to the GCS scale. Finally, the discharged disposition is classified into favorable and unfavorable outcomes. A favorable or good outcome is being discharged to home and acute rehab facilities. In contrast, outcomes such as death or discharge to the skilled nursing facility are unfavorable or poor.

Statistical Analysis

Descriptive statistics of characteristics of patients were summarized by utilization of AP and discharge disposition. Generalized linear model with a binomial distribution and logit link (i.e., logistic regression to compare the proportion of patients with good discharge outcomes after accounting for age, sex, GCS categories, ICP monitoring, mechanical ventilation, and length of hospital or NICU stay). In this project, logistic regression is used for binary response variable because the outcomes NPI and CV were both dichotomized into favorable and unfavorable outcomes. Analyses were conducted using R statistical software 4.0.

Results

Characteristics of TBI patients with AP and without AP Assessment

A total of 2998 patients were admitted with a different mechanism of trauma such as gunshot wounds, falls, assaults, and motor vehicle accidents, of whom AP assessment was done on 618 patients (20%) 8,034 times. Of those patients, 2454 (81.85%) were Caucasian, 201 (6.72%) African American, 235 (7.84%) Asian, 100 (3.33%) Native American or Alaskan, 27 (0.90%) Native Hawaiian or other Pacific Islander, 15 (0.50%) Mexican, Mexican American, and 88 (2.96%) patients did not report race (see Table 4.1).

Among patients with AP assessment, the mean age was fifty-four [Standard deviation (SD) of 21], the mean age of females was 61, and males were 51. In addition, 136 (22%) of AP patients had an mTBI, 52(8.5%) had a modTBI, and 422 (69%) had an sTBI by GCS. The mean GCS score for mTBI was 14.4 (SD 0.7), 10.3 (SD 1.1) for modTBI and 4.3 (SD 1.7) for sTBI. ICP monitoring was performed in 160 (26%) patients, and 520 (84%) were on mechanical ventilation. The mean NICU LOS was 5.5 (SD 8.2), with the mean highest of 7.8 (SD 9.8) among the modTBI patients. The modTBI patients had a greater hospital LOS of 25.5 (SD 29.9), followed by 15.8 (SD 20) among mTBI, and 14.5 (SD 20.9) for sTBI. Two hundred and thirty patients (37%) with AP assessment died, 144 (23%) were discharged home, 120 (19%) went to an acute rehabilitation center, 73 (12%) were discharged to the skilled nursing facility, and 4 (0.6%) discharged to the hospice service.

Among TBI patients who did not receive AP assessment, the mean age was 58 [SD=21], the mean age of females was 66, and the males were 55. 1,654 (69%) males, and 1,962 (65.4%) were Caucasian. A total of 1,744 (74 %) had a mild TBI, 182 (7.7%) had modTBI, and 433(18%) had a severe TBI. The mean GCS score for mTBI was 14.7 (0.6), 10.5 (1.0) for modTBI, and 4.7

(1.9) for sTBI. ICP was monitored in 50 (2.1%) patients, and 654 (27%) were on mechanical ventilation. The mean NICU LOS was 3.1 (3.4), with the mean highest of 3.4 (4.3) among the sTBI patients. The modTBI patients had greater hospital LOS of 15.3 (41.7), followed by 9.4 (13) with sTBI and 7.3 (10) with mTBI. One hundred and sixty-two (6.8%) died, 1,494 (63%) were discharged home, 224 (9.4%) went to an acute rehabilitation center, and 348 (15%) were discharged to the skilled nursing facility.

Characteristics of patients with AP assessment by discharge disposition

As shown in Table 4.2, 571 TBI patients with AP assessment were performed. The majority, 307 (54%), had poor discharge disposition. Among those with poor discharge disposition, the mean age was 63 (SD 21) compared to 45 (SD 18) for those with good discharge disposition. The mean age was 48.8 for females and 43.6 for males with good dispositions compared to a mean age of 68.4 for females and 59.7 for males among poor discharge disposition. Females constituted less than one-third of patients in good disposition and little over one-third among poor disposition.

The majority (51%) of those with poor outcomes had abnormal mean NPi, while only 13% of those with good discharge disposition had an abnormal mean NPi. Mean NPi were higher in all GCS severity classes than in patients with poor disposition, especially in severe TBI patients with a mean NPi of 2.0. Half (50%) of those with poor discharge outcomes had an abnormal mean CV, while only a third (30%) of those with good discharge disposition had abnormal mean CV. Mean CVs were higher in all GCS severity classes than in patients with poor disposition, especially in severe TBI patients with a mean CV of 0.8 mm/sec.

An external ventricular device was used to monitor ICP on 31% of patients with good dispositions compared to 21% with poor dispositions. Eighty percent of patients with good

dispositions were mechanically ventilated compared to 88% with a poor disposition. Mean NICU LOS among patients with good disposition was 5.7 compared to 5.0 in patients with a poor disposition.

Among TBI patients with a good disposition, LOS in NICU was 4.9 for mild TBI patients, 7.8 for moderate TBI patients, and 5.6 for severe TBI patients, whereas, among TBI patients with poor disposition, LOS in NICU was 6.2 for mild TBI patients, 8.3 for moderate TBI patients, and 4.3 for severe TBI patients. Mean hospital LOS among good disposition was 19 (SD 17) compared to 12 (SD 20) among poor disposition. Patients with moderate TBI had the highest mean hospital LOS of 24.6 (SD 26) and 28 (SD 35.1) among good and poor dispositions. Patients with severe TBI with poor outcomes have hospital LOS of 9 days compared to 19.9 days among severe TBI patients with a good disposition.

Initial NPi, initial CV, and discharge disposition

As shown in Table 4.3, among TBI patients with good discharge disposition, after adjusting for age, sex, GCS, ICP monitoring, mechanical ventilation, and the length of hospital and NICU stay, the patients with normal first NPi had four-fold higher odds of good discharge outcome compared to those with abnormal first NPi (see Figure 4.1). The adjusted odds ratio (OR) of initial NPi was 4.75, $p < 0.001$, 95% CI [3.05, 7.53]. Similarly, among TBI patients with good discharge disposition, the adjusted OR of initial CV was 1.96, $p < 0.005$, 95% CI [1.23, 3.15]. Age was independently associated with discharge disposition with an adjusted OR of 0.95, $p < 0.001$, 95% CI [0.93, 0.96]. The initial NPi among severe TBI had adjusted OR was 0.72, $p = 0.4$, 95% CI [0.49, 1.34], and initial CV had adjusted OR of 0.87, $p = 0.6$, 95% CI [0.50, 1.51]. The initial NPi among ICP monitored patients had an adjusted OR of 0.81, $p = 0.4$, 95%CI [0.49, 1.34], and among mechanically ventilated patients was an adjusted OR of 0.45, $p = 0.023$, 95%CI [0.22, 0.89].

In other words, TBI patients with normal initial NPi are four times more likely to have a good discharge than those with abnormal NPi. On the other hand, the patients with normal initial CV are more than two times more likely to have a good discharge than those with abnormal CV ($p = 0.005$).

Mean NPi, mean CV, and discharge disposition

A detailed description of mean NPi, mean CV, and the discharge disposition is shown in Table 4.4. Mean NPi on those with good discharge disposition more frequently had an adjusted odds ratio of 9.35, $p < 0.001$, 95% CI [5.62, 26.0]. Similarly, good discharge disposition among those with normal mean CV compared to those with abnormal mean CV was adjusted OR of 2.23, $p < 0.001$, 95% CI [1.41, 3.5]. Age was independently associated with discharge disposition with an adjusted OR of 0.94, $p <0.001$, 95% CI [0.93, 0.95].

The mean NPi among those with ICP monitoring was adjusted OR of 0.78, $p = 0.4$, 95%CI [0.46, 1.31] and the mean CV of adjusted OR of 0.8, $p = 0.4$, 95%CI [0.46, 1.39]. The calculated mean NPi among mechanically ventilated patients was adjusted OR of 0.49, $p <0.047$, 95%CI [0.24, 0.99] and the mean CV with adjusted OR of 0.55, $p = 0.11$, 95%CI [0.26, 1.14]. After accounting for age, sex, GCS, ICP, mechanical ventilation, length of NICU, and hospital stay, those with normal mean NPi had 9-fold higher odds of having a good discharge disposition ($p <0.001$). Similarly, the patients with normal mean CV compared to those with abnormal mean CV were more than twice likely to have a good discharge disposition ($p <0.001$). In addition, age was independently associated with discharge disposition ($p <0.001$].

Discussion

This project highlights a low prevalence pattern in the usage of AP (20.6%) among TBI patients despite the implementation of AP for a decade in the NICU. There is a significant underutilization of AP in TBI patients regardless of the severity scale. This data is particularly significant as this retrospective project is done at a large urban regional trauma center. Eighty percent of TBI patients admitted from January 2014 until January 2022 were not assessed using the AP device and relied on the examiner's subjective manual interpretation, which could have resulted in inconsistencies and inaccuracies in PLR readings. These variabilities among clinicians may reduce the ability to detect subtle changes and delay early intervention for worsening neurologic conditions. Multiple studies have shown the importance of consistency, accuracy, and reliability when assessing pupils of critically ill neurological patients (Meeker et al., 2005; Adoni & McNett, 2007; Boulter et al., 2021).

Neuromonitoring is an integral part of Neurocritical care to detect changes in cerebral function and identify the pathological processes to guide interventions to treat primary injuries and prevent secondary brain injuries such as cerebral edema and intracranial hypertension. However, clinical examinations can be unreliable in these patient populations due to the severity of brain injuries, sedations, and drug-induced coma. Furthermore, it can take hours to days and weeks for secondary injuries to develop. Therefore, it is important to have reproducible, objective, and accurate data to trend any subtle changes in the assessment, like blood pressure and telemonitoring readings.

Despite the accuracy and reliability of AP, there are still barriers to nurses utilizing the pupillometer. In this NICU, a few barriers might have prevented the adoption of the AP device to its fullest potential. First, there is a disassociation between TBI order sets and pupillometer order

sets, which may have resulted in a lack of standardizations of AP utility. Second, all the data are manually entered into the patients' chart, which can be time-consuming and labor-intensive. A hardware interface device reader collects data from the AP device and downloads directly to the patient's EMR, which is currently not available in the NICU. Third, due to the COVID-19 pandemic, there has been a high turnover of permanent nurses, with travel nurses being a main source of replacement. Finally, there might be a lack of education and instruction regarding its use and a perceived lack of clinical significance, further preventing routine adoption of AP in the unit.

As illustrated in Table 4.1 and Table 4.2, modTBI in both favorable and unfavorable outcomes has the most extended hospitalization compared to mTBI and sTBI. It is an unexpected finding and is clinically significant as there is a higher cost associated with longer NICU and total hospitalization stay. Baseline and interval AP data during the NICU stay may help stratify these patients in deciding on goals of care, early transfer to the floor, and planning for discharge disposition. In addition, reliable pupillary findings are useful as they will help practitioners better understand the examination trends and prognosis trajectory at the NICU. This project suggests that further research is needed to help determine if early serial AP trends can lead to early discharge from ICU, resulting in decreased NICU length of stay and lower ICU cost.

This project aimed to examine NPi and CV association with the discharge disposition; the data suggests favorable outcomes were associated with higher initial and mean NPi and Constriction velocity values. Inversely, lower initial and mean NPi and CV values were found in unfavorable outcomes. TBI patients with good discharge disposition had more frequent normal mean NPi (87%) than those with poor discharge outcomes (49%). PLR deterioration is a strong predictor of outcomes after traumatic brain injury (Klein & Depreitere, 2018; Ortega-Perez et al., 2019).

Consistent with previous studies, patients with unfavorable outcomes had lower NPi values than those with favorable outcomes. These results showed a strong association between initial NPi and CV with discharge dispositions; and even stronger positive association between mean NPi and CV with discharge dispositions. As secondary TBI develops within hours, days, to weeks; this finding highlights the importance of serial AP assessments to trend data to detect any neurological deterioration.

The AP can be used as a prognostic tool to identify a trend of an inverse relationship between decreasing pupil reactivity and increasing ICP (Al-Obaidi et al., 2020; Jhans et al., 2019; McNett et al., 2018). The clinical significance of the findings of this project, coupled with multiple prior studies, strongly recommends that NPi is a useful early parameter to consider when triaging TBI patients and could influence clinical and surgical decisions. This project also recommends that AP could serve as a signal to prompt first responders or triage clinicians to prioritize transfer and care in the presence of an abnormally low NPi.

Another purpose of this project was to examine the relationship between NPi and CV. This project found that the patients with normal mean CV are 6.99 times more likely to have a normal NPi (see Figure 4.2). The data findings have suggested that future studies may be beneficial to examine further relationships between NPi and other AP variables to understand the significance of these variables.

Limitations

This project did not consider the effects of drug interactions, such as sedatives and other confounding drugs, and neurosurgical interventions in evaluating the patients' outcomes. Second, it did not consider the spatial mechanism of trauma (focal, diffuse) and its different pathologies as

they may impact PLR changes, thus, AP readings. Third, since this is a retrospective project, it did not show a temporal association between the NPi and CV change and the clinical deterioration.

Conclusions

In this heterogeneous TBI patient population, a lower NPi and CV score on admission and during the NICU hospitalization was observed in patients with the poor neurological outcome at hospital discharge. Automated pupillometry allows rapid, precise, and objective pupillary measurements in traumatic brain injury patients and should be strongly considered for routine use in the Neurosurgical intensive care unit. This project recommends incorporating the AP order set into the TBI order set. In addition, this project strongly recommends establishing the earliest possible baseline pupillometry data upon admission (or at the Emergency Department) and serial trend over time to detect early neurological deterioration.

References

Abdelmalik, P. A., Draghic, N., & Ling, G. S. (2019). Management of moderate and severe traumatic brain injury. *Transfusion*, *59*(S2), 1529–1538. https://doi.org/10.1111/trf.15171

Abu Hamdeh, S., Shevchenko, G., Mi, J., Musunuri, S., Bergquist, J., & Marklund, N. (2018). Proteomic differences between focal and diffuse traumatic brain injury in human brain tissue. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-25060-0

Adoni, A., & McNett, M. (2007). The pupillary response in traumatic brain injury. *Journal of Trauma Nursing*, *14*(4), 191–196. https://doi.org/10.1097/01.jtn.0000318921.90627.fe

Algattas, H., & Huang, J. (2013). Traumatic brain injury pathophysiology and treatments: Early, intermediate, and late phases post-injury. *International Journal of Molecular Sciences*, *15*(1), 309–341. https://doi.org/10.3390/ijms15010309

Alluri, H., Wiggins-Dohlvik, K., Davis, M. L., Huang, J. H., & Tharakan, B. (2015). Blood–brain barrier dysfunction following traumatic brain injury. *Metabolic Brain Disease*, *30*(5), 1093–1104. https://doi.org/10.1007/s11011-015-9651-7

Al-Obaidi, S., Atem, F., Stutzman, S. E., Aiyagari, V., & Olson, D. M. (2020). Investigating the association between eye colour and the neurological pupil index. *Australian Critical Care*, *33*(5), 436–440. https://doi.org/10.1016/j.aucc.2019.10.001

Anderson, E. S., Greenwood-Ericksen, M., Wang, N., & Dworkis, D. A. (2019). Closing the gap: Improving access to trauma care in New Mexico (2007–2017). *The American Journal of Emergency Medicine*, *37*(11), 2028–2034. https://doi.org/10.1016/j.ajem.2019.02.030

Anderson, M., Elmer, J., Shutter, L., Puccio, A., & Alexander, S. (2018). Integrating quantitative pupillometry into regular care in a neurotrauma intensive care unit. *Journal of Neuroscience Nursing*, *50*(1), 30–36. https://doi.org/10.1097/jnn.0000000000000333

Aoun, S. G., Stutzman, S. E., Vo, P.-U. N., El Ahmadieh, T. Y., Osman, M., Neeley, O., Plitt, A., Caruso, J. P., Aiyagari, V., Atem, F., Welch, B. G., White, J. A., Batjer, H., & Olson, D. M. (2020). Detection of delayed cerebral ischemia using objective pupillometry in patients with aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgery*, *132*(1), 27–32. https://doi.org/10.3171/2018.9.jns181928

Belliveau, A. P., Sonami, A. N., & Dossani, R. H. (2021). Pupillary light reflex. *StatPearls Publishing,Treasure Island (FL)*. https://www.ncbi.nlm.nih.gov/books/NBK537180/?report=classic

Boulter, J. H., Shields, M. M., Meister, M. R., Murtha, G., Curry, B. P., & Dengler, B. A. (2021). The expanding role of quantitative pupillometry in the evaluation and management of traumatic brain injury. *Frontiers in Neurology*, *12*. https://doi.org/10.3389/fneur.2021.685313

Brennan, P. M., Murray, G. D., & Teasdale, G. M. (2018). Simplifying the use of prognostic information in traumatic brain injury. part 1: The GCS-pupils score: An extended index of clinical severity. *Journal of Neurosurgery*, *128*(6), 1612–1620. https://doi.org/10.3171/2017.12.jns172780

Capizzi, A., Woo, J., & Verduzco-Gutierrez, M. (2020). Traumatic brain injury. *Medical Clinics of North America*, *104*(2), 213–238. https://doi.org/10.1016/j.mcna.2019.11.001

Centers for Disease Control and Prevention (2019). Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. *Centers for Disease Control and Prevention, U.S. Department of Health and Human Services*.https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-Report-FINAL_508.pdf.

Centers for Disease Control and Prevention (2022). Surveillance Report of Traumatic Brain Injury-related Deaths by Age Group, Sex, and Mechanism of Injury—United States, 2018 and 2019. *Centers for Disease Control and Prevention, U.S. Department of Health, and Human services.* https://www.cdc.gov/traumaticbraininjury/pdf/TBI-surveillance-report-2018-2019-508.pdf.

Chestnut, R. M., Marshall, L. F., Klauber, M. R., Blunt, B. A., Baldwin, N., Eisenberg, H. M., Jane, J. A., Marmarou, A., & Foulkes, M. A. (1993). The role of secondary brain injury in determining outcome from severe head injury. *The Journal of Trauma: Injury, Infection, and Critical Care*, *34*(2), 216–222. https://doi.org/10.1097/00005373-199302000-00006

Chodobski, A., Zink, B. J., & Szmydynger-Chodobska, J. (2011). Blood–brain barrier pathophysiology in traumatic brain injury. *Translational Stroke Research*, *2*(4), 492–516. https://doi.org/10.1007/s12975-011-0125-x

Ciuffreda, K. J., Joshi, N. R., & Truong, J. Q. (2017). Understanding the effects of mild traumatic brain injury on the pupillary light reflex. *Concussion*, *2*(3), CNC36. https://doi.org/10.2217/cnc-2016-0029

Couret, D., Boumaza, D., Grisotto, C., Triglia, T., Pellegrini, L., Ocquidant, P., Bruder, N. J., & Velly, L. J. (2016). Reliability of standard pupillometry practice in neurocritical care: An observational, double-blinded study. *Critical Care*, *20*(1). https://doi.org/10.1186/s13054-016-1239-z

Dash, H., & Chavali, S. (2018). Management of traumatic brain injury patients. *Korean Journal of Anesthesiology*, *71*(1), 12. https://doi.org/10.4097/kjae.2018.71.1.12

Daugherty, J., Waltzman, D., Sarmiento, K., & Xu, L. (2019). Traumatic brain injury–related deaths by race/ethnicity, sex, intent, and mechanism of injury — united states, 2000–

2017. *MMWR. Morbidity and Mortality Weekly Report*, *68*(46), 1050–1056. https://doi.org/10.15585/mmwr.mm6846a2

Davceva, N., Sivevski, A., & Basheska, N. (2017). Traumatic axonal injury, a clinical-pathological correlation. *Journal of Forensic and Legal Medicine*, *48*, 35–40. https://doi.org/10.1016/j.jflm.2017.04.004

Dewan, M. C., Rattani, A., Gupta, S., Baticulon, R. E., Hung, Y.-C., Punchak, M., Agrawal, A., Adeleye, A. O., Shrime, M. G., Rubiano, A. M., Rosenfeld, J. V., & Park, K. B. (2019). Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery*, *130*(4), 1080–1097. https://doi.org/10.3171/2017.10.jns17352

El Ahmadieh, T. Y., Bedros, N., Stutzman, S. E., Nyancho, D., Venkatachalam, A. M., MacAllister, M., Ban, V., Dahdaleh, N. S., Aiyagari, V., Figueroa, S., White, J. A., Batjer, H., Bagley, C. A., Olson, D. M., & Aoun, S. G. (2021). Automated pupillometry as a triage and assessment tool in patients with traumatic brain injury. *World Neurosurgery*, *145*, e163–e169. https://doi.org/10.1016/j.wneu.2020.09.152

Emelifeonwu, J. A., Reid, K., Rhodes, J., & Myles, L. (2018). Saved by the pupillometer! – a role for pupillometry in the acute assessment of patients with traumatic brain injuries? *Brain Injury*, *32*(5), 675–677. https://doi.org/10.1080/02699052.2018.1429021

Fakharian, E., Banaee, S., Yazdanpanah, H., & Momeny, M. (2018). Head injury mechanisms. In *Traumatic brain injury - pathobiology, advanced diagnostics, and acute management*. InTech. https://doi.org/10.5772/intechopen.75454

Fatima, N., Shuaib, A., Chughtai, T., Ayyad, A., & Saqqur, M. (2019). The role of transcranial doppler in traumatic brain injury: A systemic review and meta-analysis. *Asian Journal of Neurosurgery*, *14*(3), 626. https://doi.org/10.4103/ajns.ajns_42_19

Galgano, M., Toshkezi, G., Qiu, X., Russell, T., Chin, L., & Zhao, L.-R. (2017). Traumatic brain injury. *Cell Transplantation*, *26*(7), 1118–1130. https://doi.org/10.1177/0963689717714102

Giede-Jeppe, A., Sprügel, M. I., Huttner, H. B., Borutta, M., Kuramatsu, J. B., Hoelter, P., Engelhorn, T., Schwab, S., & Koehn, J. (2020). Automated pupillometry identifies absence of intracranial pressure elevation in intracerebral hemorrhage patients. *Neurocritical Care*, *35*(1), 210–220. https://doi.org/10.1007/s12028-020-01146-4

Glasgow coma scale. (2015). In *Encyclopedia of trauma care* (pp. 702–702). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-29613-0_100687

Goldberg, G., & Glazer, D. (2020). Basic brain neuroscience and pathophysiology. In *Brain injury medicine* (pp. 28–42.e2). Elsevier. https://doi.org/10.1016/b978-0-323-65385-5.00011-1

Gu, J., Wu, H., Chen, X., Feng, J., Gao, G., Jiang, J., & Mao, Q. (2020). Intracranial pressure during external ventricular drainage weaning is an outcome predictor of traumatic brain injury. *BioMed Research International*, *2020*, 1–7. https://doi.org/10.1155/2020/8379134

Haarbauer-Krupa, J., Pugh, M., Prager, E. M., Harmon, N., Wolfe, J., & Yaffe, K. (2021). Epidemiology of chronic effects of traumatic brain injury. *Journal of Neurotrauma*, *38*(23), 3235–3247. https://doi.org/10.1089/neu.2021.0062

Hadanny, A., & Efrati, S. (2015). Oxygen - a limiting factor for brain recovery. *Critical Care*, *19*(1). https://doi.org/10.1186/s13054-015-1034-2

Hart, T., Novack, T. A., Temkin, N., Barber, J., Dikmen, S. S., Diaz-Arrastia, R., Ricker, J., Hesdorffer, D. C., Jallo, J., Hsu, N. H., & Zafonte, R. (2016). Duration of posttraumatic amnesia predicts neuropsychological and global outcome in complicated mild traumatic

brain injury. *Journal of Head Trauma Rehabilitation*, *31*(6), E1–E9. https://doi.org/10.1097/htr.0000000000000210

Hawryluk, G. W., & Manley, G. T. (2015). Classification of traumatic brain injury. In *Handbook of clinical neurology* (pp. 15–21). Elsevier. https://doi.org/10.1016/b978-0-444-52892-6.00002-7

Humphreys, I., Wood, Phillips, C., & Macey. (2013). The costs of traumatic brain injury: A literature review. *ClinicoEconomics and Outcomes Research*, 281. https://doi.org/10.2147/ceor.s44625

Jahns, F.-P., Miroz, J., Messerer, M., Daniel, R. T., Taccone, F., Eckert, P., & Oddo, M. (2019). Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. *Critical Care*, *23*(1). https://doi.org/10.1186/s13054-019-2436-3

Jassam, Y. N., Izzy, S., Whalen, M., McGavern, D. B., & El Khoury, J. (2017). Neuroimmunology of traumatic brain injury: Time for a paradigm shift. *Neuron*, *95*(6), 1246–1265. https://doi.org/10.1016/j.neuron.2017.07.010

Johns, P. (2016). Functional neuroanatomy. In *Clinical neuroscience* (pp. 27–47). Elsevier. https://doi.org/10.1016/b978-0-443-10321-6.00003-5

Kadry, H., Noorani, B., & Cucullo, L. (2020). A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids and Barriers of the CNS*, *17*(1). https://doi.org/10.1186/s12987-020-00230-3

Kalisvaart, A. J., Wilkinson, C. M., Gu, S., Kung, T. C., Yager, J., Winship, I. R., van Landeghem, F. H., & Colbourne, F. (2020). An update to the monro–kellie doctrine to

reflect tissue compliance after severe ischemic and hemorrhagic stroke. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-78880-4

Kaur, P., & Sharma, S. (2018). Recent advances in pathophysiology of traumatic brain injury. *Current Neuropharmacology*, *16*(8), 1224–1238. https://doi.org/10.2174/1570159x15666170613083606

Kerr, R. G., Bacon, A. M., Baker, L. L., Gehrke, J. S., Hahn, K., Lillegraven, C. L., Renner, C., & Spilman, S. K. (2016). Underestimation of pupil size by critical care and neurosurgical nurses. *American Journal of Critical Care*, *25*(3), 213–219. https://doi.org/10.4037/ajcc2016554

Khellaf, A., Khan, D., & Helmy, A. (2019). Recent advances in traumatic brain injury. *Journal of Neurology*, *266*(11), 2878–2889. https://doi.org/10.1007/s00415-019-09541-4

Kim, T., Park, S.-H., Jeong, H.-B., Ha, E., Cho, W., Kang, H.-S., Kim, J., & Ko, S.-B. (2020). Neurological pupil index as an indicator of neurological worsening in large hemispheric strokes. *Neurocritical Care*, *33*(2), 575–581. https://doi.org/10.1007/s12028-020-00936-0

Kinoshita, K. (2016). Traumatic brain injury: Pathophysiology for neurocritical care. *Journal of Intensive Care*, *4*(1). https://doi.org/10.1186/s40560-016-0138-3

Klein, S., & Depreitere, B. (2018). What determines outcome in patients that suffer raised intracranial pressure after traumatic brain injury? In *Acta neurochirurgica supplement* (pp. 51–54). Springer International Publishing. https://doi.org/10.1007/978-3-319-65798-1_11

Ladak, A., Enam, S., & Ibrahim, M. (2019). A review of the molecular mechanisms of traumatic brain injury. *World Neurosurgery*, *131*, 126–132. https://doi.org/10.1016/j.wneu.2019.07.039

Larson, M. D., & Behrends, M. (2015). Portable infrared pupillometry. *Anesthesia & Analgesia*, *120*(6), 1242–1253. https://doi.org/10.1213/ane.0000000000000314

Lee, M., Mitra, B., Pui, J., & Fitzgerald, M. (2018). The use and uptake of pupillometers in the intensive care unit. *Australian Critical Care*, *31*(4), 199–203. https://doi.org/10.1016/j.aucc.2017.06.003

Lindberg, R. (2020). Nontraumatic brain injury. In *Brain injury medicine* (pp. 332–336.e2). Elsevier. https://doi.org/10.1016/b978-0-323-65385-5.00062-7

Lussier, B. L., Olson, D. M., & Aiyagari, V. (2019). Automated pupillometry in neurocritical care: Research and practice. *Current Neurology and Neuroscience Reports*, *19*(10). https://doi.org/10.1007/s11910-019-0994-z

Lynch G. (2018). Using Pupillometry to Assess the Atypical Pupillary Light Reflex and LC-NE System in ASD. *Behavioral sciences*, *8*(11), 108. https://doi.org/10.3390/bs8110108

Ma, J., Zhang, K., Wang, Z., & Chen, G. (2016). Progress of research on diffuse axonal injury after traumatic brain injury. *Neural Plasticity*, *2016*, 1–7. https://doi.org/10.1155/2016/9746313

Maas, A. R., Menon, D. K., Adelson, P., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chestnut, R. M., Citerio, G., Coburn, M., Cooper, D., Crowder, A., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J. P., Duhaime, A.-C.,...Zumbo, F. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology*, *16*(12), 987–1048. https://doi.org/10.1016/s1474-4422(17)30371-x

Majdan, M., Steyerberg, E. W., Nieboer, D., Mauritz, W., Rusnak, M., & Lingsma, H. F. (2015). Glasgow coma scale motor score and pupillary reaction to predict six-month mortality in

patients with traumatic brain injury: Comparison of field and admission assessment. *Journal of Neurotrauma*, *32*(2), 101–108. https://doi.org/10.1089/neu.2014.3438

Maldonado, K. A., & Alsayouri, K. (2021). *Physiology, Brain.* In StatPearls. StatPearls Publishing.

Martini, R., Orfanakis, A., & Brambrink, A. (2022). Intracranial pressure monitoring. *Monitoring the Nervous System for Anesthesiologists and Other Health Care Professionals*, 243–252. https://doi.org/10.1007/978-3-319-46542-5_15

Master, C. L., Podolak, O. E., Ciuffreda, K. J., Metzger, K. B., Joshi, N. R., McDonald, C. C., Margulies, S. S., Grady, M. F., & Arbogast, K. B. (2020). Utility of pupillary light reflex metrics as a physiologic biomarker for adolescent sport-related concussion. *JAMA Ophthalmology*, *138*(11), 1135. https://doi.org/10.1001/jamaophthalmol.2020.3466

Mazhar, K., Olson, D. M., Atem, F. D., Stutzman, S. E., Moreno, J., Venkatachalam, A., & Aiyagari, V. (2021). Supratentorial intracerebral hemorrhage volume and other ct variables predict the neurological pupil index. *Clinical Neurology and Neurosurgery*, *200*, 106410. https://doi.org/10.1016/j.clineuro.2020.106410

Mckee, A. C., & Daneshvar, D. H. (2015). The neuropathology of traumatic brain injury. In *Handbook of clinical neurology* (pp. 45–66). Elsevier. https://doi.org/10.1016/b978-0-444-52892-6.00004-0

McNett, M., Moran, C., Grimm, D., & Gianakis, A. (2018). Pupillometry trends in the setting of increased intracranial pressure. *Journal of Neuroscience Nursing*, *50*(6), 357–361. https://doi.org/10.1097/jnn.0000000000000401

Meeker, M., Du, R., Bacchetti, P., Privitera, C. M., Larson, M. D., Holland, M. C., & Manley, G. (2005). Pupil examination. *Journal of Neuroscience Nursing*, *37*(1), 34–40. https://doi.org/10.1097/01376517-200502000-00006

Mondello, S., Papa, L., Buki, A., Bullock, M., Czeiter, E., Tortella, F. C., Wang, K. K., & Hayes, R. L. (2011). Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: A case control study. *Critical Care*, *15*(3), R156. https://doi.org/10.1186/cc10286

Naseri Alavi, S., Salehpour, F., Bazzazi, A., Aghazadeh, J., Hasanloei, A., Pasban, K., & Mirzaei, F. (2018). What do you expect from patients with severe head trauma? *Asian Journal of Neurosurgery*, *13*(3), 660. https://doi.org/10.4103/ajns.ajns_260_16

Ng, S., & Lee, A. (2019). Traumatic brain injuries: Pathophysiology and potential therapeutic targets. *Frontiers in Cellular Neuroscience*, *13*. https://doi.org/10.3389/fncel.2019.00528

Neurooptics (2021). Trending pupil size and reactivity in the critical care patients. https://neurOptics.com/critical-care-info/

Olson, D. M., Stutzman, S., Saju, C., Wilson, M., Zhao, W., & Aiyagari, V. (2015). Interrater reliability of pupillary assessments. *Neurocritical Care*, *24*(2), 251–257. https://doi.org/10.1007/s12028-015-0182-1

Ortega-Perez, S., Shoyombo, I., Aiyagari, V., Atem, F., Hill, M., Stutzman, S. E., & Olson, D. M. (2019). Pupillary light reflex variability as a predictor of clinical outcomes in subarachnoid hemorrhage. *Journal of Neuroscience Nursing*, *51*(4), 171–175. https://doi.org/10.1097/jnn.0000000000000443

Papangelou, A., Zink, E. K., Chang, W.-T. W., Frattalone, A., Gergen, D., Gottschalk, A., & Geocadin, R. G. (2018). Automated pupillometry and detection of clinical transtentorial

brain herniation: A case series. *Military Medicine*, *183*(1-2), e113–e121. https://doi.org/10.1093/milmed/usx018

Patel, K. G., & Sabini, R. C. (2018). Safety of osteopathic cranial manipulative medicine as an adjunct to conventional postconcussion symptom management: A pilot study. *Journal of Osteopathic Medicine*, *118*(6), 403–409. https://doi.org/10.7556/jaoa.2018.061

Ponsford, J., Sloan, S., & Snow, P. (2012). *Traumatic brain injury: Rehabilitation for everyday adaptive living* (2nd ed.). Psychology Press.

Roy, D., Peters, M. E., Everett, A. D., Leoutsakos, J.-M., Yan, H., Rao, V., T. Bechtold, K., Sair, H. I., Van Meter, T., Falk, H., Vassila, A., Hall, A., Ofoche, U., Akbari, F., Lyketsos, C., & Korley, F. (2020). Loss of consciousness and altered mental state as predictors of functional recovery within 6 months following mild traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *32*(2), 132–138. https://doi.org/10.1176/appi.neuropsych.18120379

Saatman, K. E., Duhaime, A.-C., Bullock, R., Maas, A. I., Valadka, A., & Manley, G. T. (2008). Classification of traumatic brain injury for targeted therapies. *Journal of Neurotrauma*, *25*(7), 719–738. https://doi.org/10.1089/neu.2008.0586

Scholten, A., Haagsma, J., Andriessen, T., Vos, P., Steyerberg, E., van Beeck, E., & Polinder, S. (2015). Health-related quality of life after mild, moderate and severe traumatic brain injury: Patterns and predictors of suboptimal functioning during the first year after injury. *Injury*, *46*(4), 616–624. https://doi.org/10.1016/j.injury.2014.10.064

Schulman, J. (2002). State level estimates of the incidence and economic burden of head injuries stemming from non-universal use of bicycle helmets. *Injury Prevention*, *8*(1), 47–52. https://doi.org/10.1136/ip.8.1.47

Shoyombo, I., Aiyagari, V., Stutzman, S. E., Atem, F., Hill, M., Figueroa, S. A., Miller, C., Howard, A., & Olson, D. M. (2018). Understanding the relationship between the neurologic pupil index and constriction velocity values. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-25477-7

Simon, S. D. (2022). Centers for disease control and prevention. In *Encyclopedia of big data* (pp. 158–161). Springer International Publishing. https://doi.org/10.1007/978-3-319-32010-6_258

Standring, S. (2012). Overview of the nervous system. In *Gray's anatomy* (pp. 225–236). Elsevier. https://doi.org/10.1016/b978-0-443-06684-9.50023-8

Stocchetti, N., Carbonara, M., Citerio, G., Ercole, A., Skrifvars, M. B., Smielewski, P., Zoerle, T., & Menon, D. K. (2017). Severe traumatic brain injury: Targeted management in the intensive care unit. *The Lancet Neurology*, *16*(6), 452–464. https://doi.org/10.1016/s1474-4422(17)30118-7

Sulhan, S., Lyon, K. A., Shapiro, L. A., & Huang, J. H. (2018). Neuroinflammation and blood-brain barrier disruption following traumatic brain injury: Pathophysiology and potential therapeutic targets. *Journal of Neuroscience Research*, *98*(1), 19–28. https://doi.org/10.1002/jnr.24331

Telano L. N., & Baker S (2021). Physiology, Cerebral Spinal Fluid. *StatPearls Publishing, Treasure Island (FL)*. https://www.ncbi.nlm.nih.gov/books/NBK519007/

Tamura, T., Namiki, J., Sugawara, Y., Sekine, K., Yo, K., Kanaya, T., Yokobori, S., Abe, T., Yokota, H., & Sasaki, J. (2020). Early outcome prediction with quantitative pupillary response parameters after out-of-hospital cardiac arrest: A multicenter prospective

observational study. *PLOS ONE*, *15*(3), e0228224. https://doi.org/10.1371/journal.pone.0228224

Taylor, W. R., Chen, J. W., Meltzer, H., Gennarelli, T. A., Kelbch, C., Knowlton, S., Richardson, J., Lutch, M. J., Farin, A., Hults, K. N., & Marshall, L. F. (2003). Quantitative pupillometry, a new technology: Normative data and preliminary observations in patients with acute head injury. *Journal of Neurosurgery*, *98*(1), 205–213. https://doi.org/10.3171/jns.2003.98.1.0205

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. *The Lancet*, *304*(7872), 81–84. https://doi.org/10.1016/s0140-6736(74)91639-0

The epidemiology and pathophysiology of traumatic brain injury. (2021). In *Traumatic brain injury* (pp. 21–44). CRC Press. https://doi.org/10.1201/9780203501740-6

Vos, P. E. (2011). Biomarkers of focal and diffuse traumatic brain injury. *Critical Care*, *15*(4), 183. https://doi.org/10.1186/cc10290

Weiland, J., Beez, A., Westermaier, T., Kunze, E., Sirén, A.-L., & Lilla, N. (2021). Neuroprotective strategies in aneurysmal subarachnoid hemorrhage (asah). *International Journal of Molecular Sciences*, *22*(11), 5442. https://doi.org/10.3390/ijms22115442

Xiong, Y., Mahmood, A., & Chopp, M. (2018). Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. *Chinese Journal of Traumatology*, *21*(3), 137–151. https://doi.org/10.1016/j.cjtee.2018.02.003

Yoo, H., & Mihaila, D. M. (2021). Neuroanatomy, pupillary light reflexes and pathway. *StatPearls Publishing*, *Treasure Island (FL)*. http://europepmc.org/books/NBK553169

Zafar, S. F., & Suarez, J. I. (2014a). Automated pupillometer for monitoring the critically ill patient: A critical appraisal. *Journal of Critical Care*, *29*(4), 599–603. https://doi.org/10.1016/j.jcrc.2014.01.012

Zafar, S. F., & Suarez, J. I. (2014b). Automated pupillometer for monitoring the critically ill patient: A critical appraisal. *Journal of Critical Care*, *29*(4), 599–603. https://doi.org/10.1016/j.jcrc.2014.01.012

Zakaria, Z., Abdullah, M., Abdul Halim, S., Ghani, A., Idris, Z., & Abdullah, J. (2020). The neurological exam of a comatose patient: An essential practical guide. *Malaysian Journal of Medical Sciences*, *27*(5), 108–123. https://doi.org/10.21315/mjms2020.27.5.11

Appendix A

Figure 1.1

A Large Urban Center Policies on An Automated Pupillometer Utilization

NeurOptics NPi®-200 Pupillometer

Purpose: Used to objectively quantify the rate of pupil reactivity and pupil size .

Performed by: Critical Care RNs who have received training and education regarding using the pupillometer and interpretation of the findings.

Equipment: Clean gloves

Pupillometer NPi®-200

SmartGuard™ (previously called Headrest)(NeurOptics)

Socket barcode scanner

Antiseptic wipes

Clear plastic bag (for isolation rooms)

Alcohol wipes (optional)

Policies: 1. The pupillometer does not replace the usual pupil assessment with a penlight or flashlight. The pupillometer is an adjunct to the usual pupil assessment.

2. Pupillometer results are to be documented in the electronic medical record (EMR).

3. Each patient is to have their own SmartGuard™.

4. The pupillometer is to be cleaned after each patient use.

5. No provider order is required to use the pupillometer. Exercise caution in patients with periorbital or eye trauma.

Recommendation: Patients who may benefit from the use of the pupillometer include those who have:

1. Severe traumatic brain injury or unstable intracranial dynamics (increased ICP, decreased CPP, and low pbtO2)
2. Glasgow Coma Score < 8
3. Severe cerebral vasospasm related to aneurysmal or traumatic subarachnoid hemorrhage
4. Unequal pupils
5. Dark eyes and difficult to see pupils
6. Continuous sedation or drug-induced coma which does not allow for awakening for neurologic assessment.

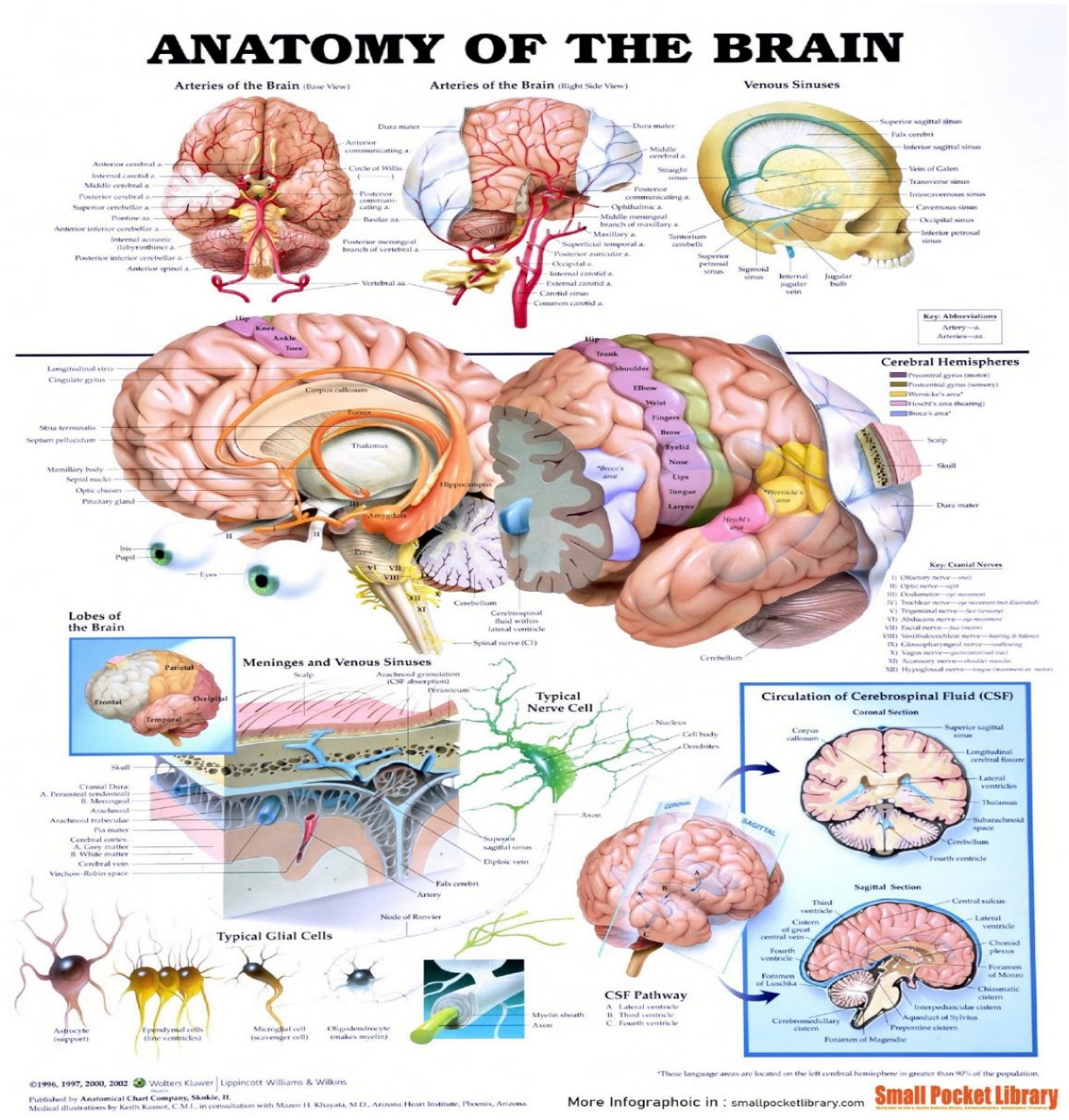
Frequency of pupillometer measurement may vary depending on patient's condition and clinical judgment

Note. ICP= Intracranial pressure, CPP=Cerebral perfusion pressure, pbtO2= Continuous brain tissue oxygen.

Appendix B

Figure 2.1

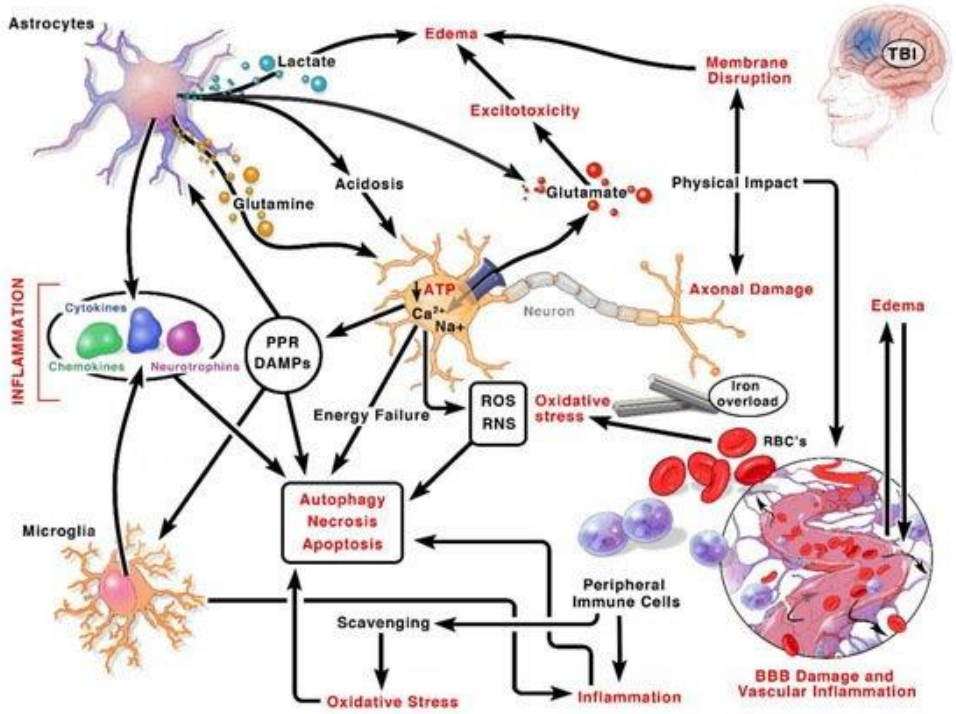
Anatomy and Functions of Brain



Note. From "Anatomical Chart Company" by Kasnot, K & Khayata, M. H., 2002. (https://i.imgur.com/nh0oSC5.jpg).Copyright by Wolters Kluwer Lippincott Williams and Wilkins.

Figure 2.2

A Schematic Flowchart of Pathophysiology of Traumatic Brain Injury



Note. DAMP: Damage associated molecular patterns; PRR: Pattern recognition receptors; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; RBC: Red blood cells; Na^{+}: Sodium ion; Ca^{2+}: Calcium ion; ATP: Adenosine triphosphate; TBI: Traumatic brain injury.

From "Revisiting Traumatic Brain Injury: From Molecular Mechanisms to Therapeutic Interventions." by Jarrahi A, Braun M, Ahluwalia M, Gupta RV, Wilson M, Munie S, Ahluwalia P, Vender JR, Vale FL, Dhandapani KM, Vaibhav K. Revisiting Traumatic Brain Injury: From Molecular Mechanisms to Therapeutic Interventions. *Biomedicines*. 2020; 8(10):389. (https://doi.org/10.3390/biomedicines8100389). Copyright 2020 by Biomedicines.

Appendix B

Figure 2.3

Classification of Glasgow Coma Scale

Glasgow Coma Scale		
Eye Response	Open Spontaneously	4
	Open to Verbal command	3
	Open in response to pain	2
	No response	1
Verbal Response	Talking / Orientated	5
	Confused speech / Disorientated	4
	Inappropriate Words	3
	Incomprehensible sounds	2
	No response	1
Motor Response	Obeys commands	6
	Localizes pain	5
	Withdraws from pain	4
	Abnormal flexion	3
	Extension	2
	No response	1

Note. From "Assessment of Coma and Impaired Consciousness – A Practical Scale" in the Lancet in 1974 by Teasdale, G., & Jennett, B. Assessment of coma and impaired consciousness. *The Lancet*, *304*(7872), 81–84. (https://doi.org/10.1016/s0140-6736(74)91639-0). Copyrighted by The Lancet.

Figure 2.4

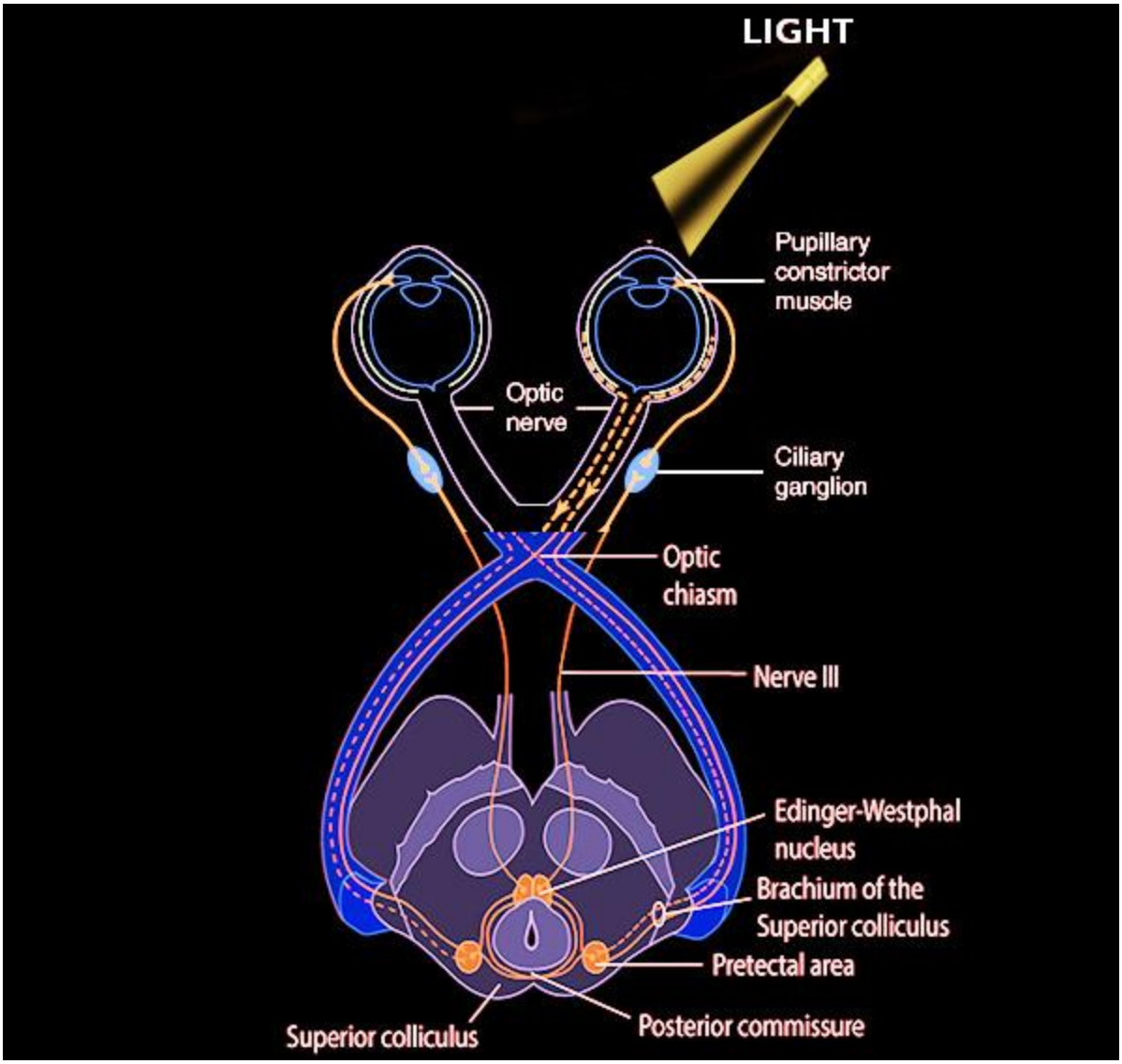
Classification of Traumatic Brain Injury by Different Measures of Severity

Classification System For Traumatic Brain Injury			
Classification	Duration Of Unconsciousness	Glasgow Coma Scale	Post-Traumatic Amnesia
Mild	<30 Minutes	13-15	<24 Hours
Moderate	30 Minutes-24 Hours	9-12	1-7 Days
Severe	>24 Hours	3-8	>7 Days

Note. From "Neuropsychological Evaluation of Traumatic Brain Injury: The Definitive Guide" by Gharibian, E. Garibian, E. (n.d). Neuropsychological Evaluation of Traumatic Brain Injury: The Definitive Guide. (https://verdugopsych.com/neuropsychological-evaluation-of-traumatic-brain-injury/).

Figure 2.5

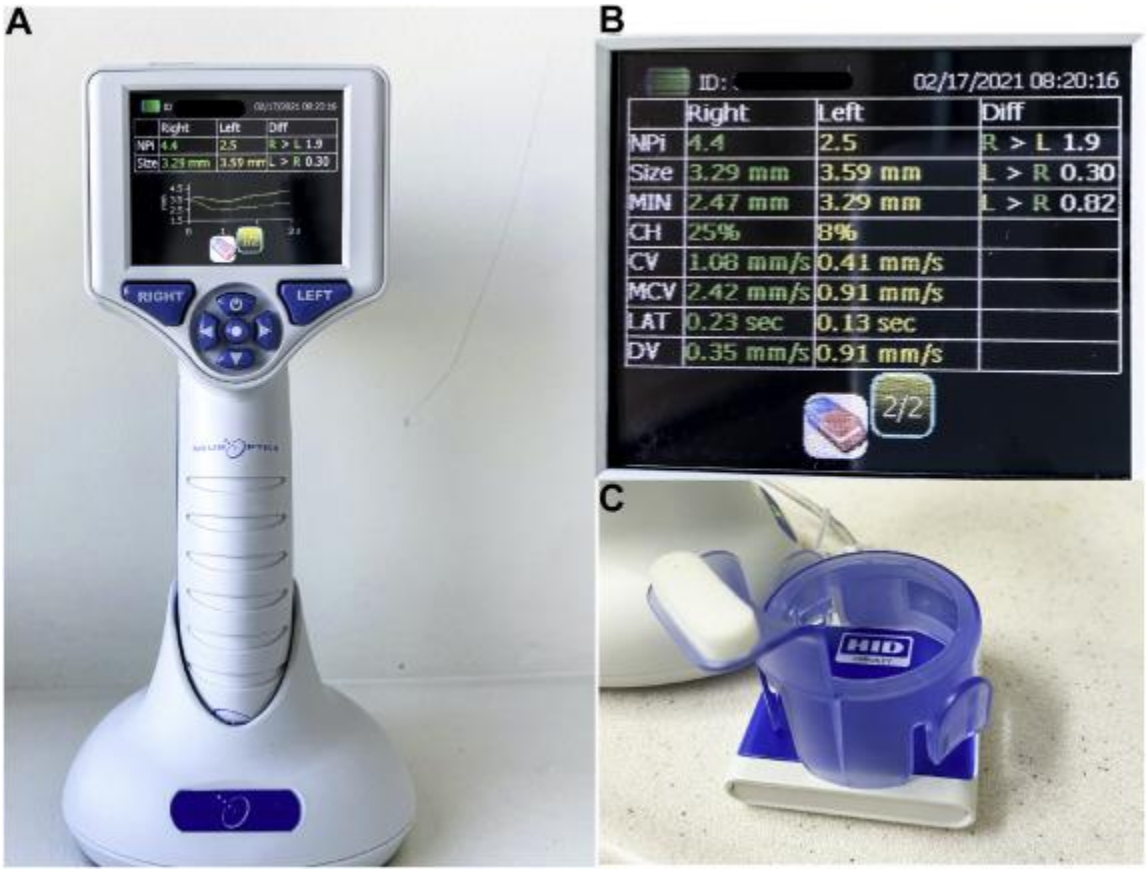
Anatomic Description of Pupillary Light Reflex Pathway



Note. From "Pupillary light reflex" by Belliveau, A. P., Sonami, A. N., & Dossani, R. H. (2021). Pupillary light reflex. *StatPearls Publishing,Treasure Island (FL)*. (https://www.ncbi.nlm.nih.gov/books/NBK537180/?report=classic)

Figure 2.6

NeurOptics NPi®-200 Automated Pupillometer



Note. From "Trending pupil size and reactivity in the critical care patients." NeurOptics (2021). Trending pupil size and reactivity in the critical care patients. (https://neurOptics.com/critical-care-info/). Copyright 2021 by NeurOptics.

Figure 2.7

Description of Variables Reported by Automated Pupillometer

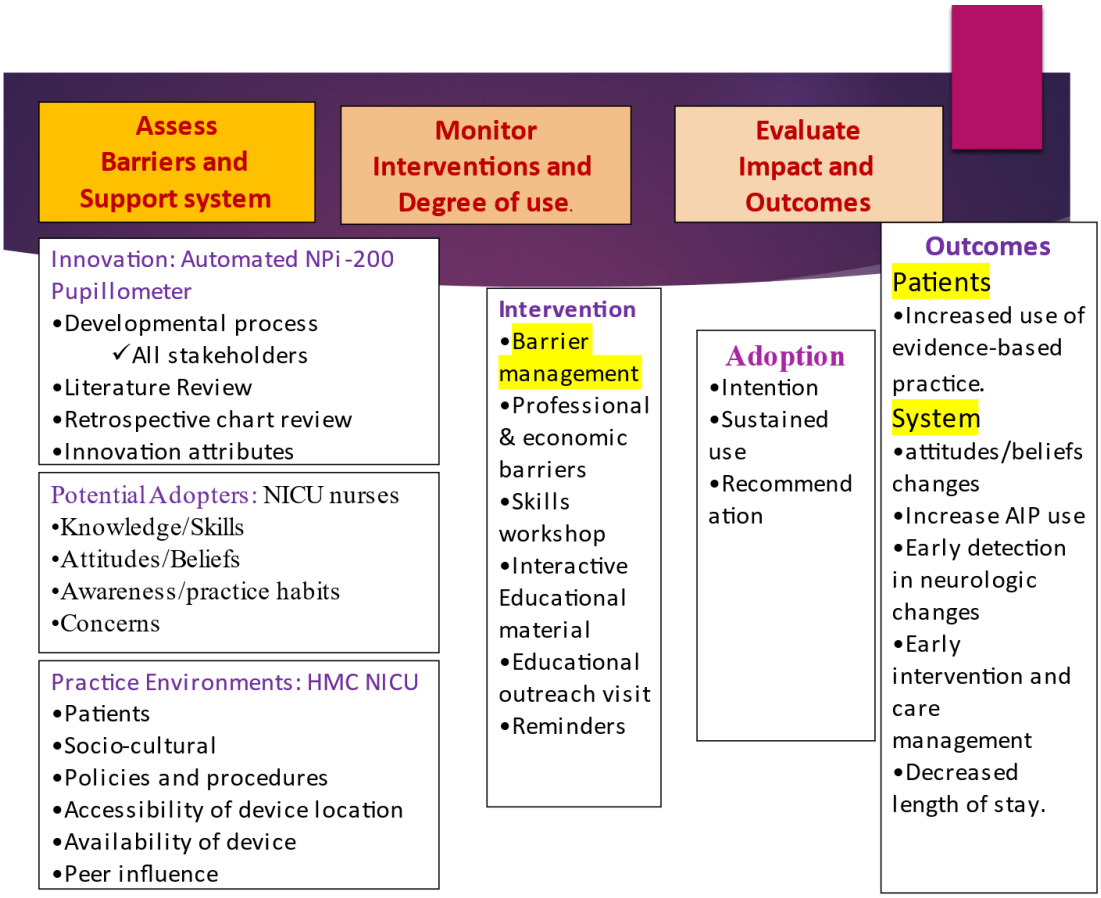
Variable reported by pupillometer	Unit of measure	Definition
Pupil Min/Max Size	mm	The minimum pupil size is the pupil size at the peak of the constriction. Maximum pupil size is the initial resting pupil size, and is defined by the mean pupil size during the latent period.
Constriction % or Percentage Change	%	The constriction percentage is defined as maximum size minus minimum size divided by the maximum size.
Latency	seconds	The time difference between the initiation of retinal light stimulation and the onset of pupillary constriction.
Constriction Velocity	mm/sec	The amount of the constriction divided by the duration of the constriction; this results in an average velocity
Maximum Constriction Velocity	mm/sec	The peak value of the velocity during constriction; this is larger than the previous average velocity.
Dilation Velocity	mm/sec	The amount of pupil size recovery (after the constriction) divided by the duration of the recovery
NPi (Neurological Pupil index)	Scalar value	Algorithm that takes all variables above as inputs and compares to normative model to give a composite score of pupillary response

Note. From "Trending pupil size and reactivity in the critical care patients." NeurOptics (2021). Trending pupil size and reactivity in the critical care patients. (https://neurOptics.com/critical-care-info/). Copyright 2021 by NeurOptics.

Appendix C

Figure 3.1

Theoretical Framework: The Ottawa Model of Research Use



Note. Adapted from "Innovations in knowledge transfer and continuity of care" by Graham, I.D., & Logan. J. (2004). *Canadian Journal of Nursing Research, 36*(2), 89-103. The essential elements: (1) evidence-based innovation, (2) potential adopters, (3) the practice environment, (4) implementation of interventions, (5) adoption of the innovation, (6) outcomes resulting from the implementation of the innovation.

Appendix D

Table 4.1

Characteristics of Traumatic Brain Injury Patients with and without Automated Pupillometer Assessment

	Pupillometer	
Characteristic	No, N = 2,380[1]	Yes, N = 618[1]
Age	58 (21)	54 (21)
Female	66 (19)	61 (20)
Male	55 (21)	51 (21)
Sex		
Female	726 (31%)	173 (28%)
Male	1,654 (69%)	445 (72%)
Ethnicity		
Hispanic or Latino	197	69
Not Hispanic or Latino	2219	530
Declined/Unknown	61	44
Race		
White	1962 (65.4%)	492 (16.4%)
Black or African American	160 (5.3%)	41 (1.4%)
Asian	182 (6%)	53 (1.8%)
Native American or Alaskan	78 (2.6%)	22 (0.7%)
Native Hawaiian or other Pacific Islander	23 (0.8%)	4 (0.1%)
Mexican or Mexican American	15 (0.5%)	0 (0%)
Unknown	57 (1.9%)	31 (1.0%)
Glasgow Coma Scale		
Mild (13-15)	1,744 (74%)	136 (22%)
Moderate (9-12)	182 (7.7%)	52 (8.5%)
Severe (3-8)	433 (18%)	422 (69%)
Average GSC score		
Mild	14.7 (0.6)	14.4 (0.7)
Moderate	10.5 (1.0)	10.3 (1.1)
Severe	4.7 (1.9)	4.3 (1.7)
ICP Monitoring		
No	2,330 (98%)	458 (74%)
Yes	50 (2.1%)	160 (26%)
Mechanical Ventilation		
No	1,726 (73%)	98 (16%)
Yes	654 (27%)	520 (84%)
NICU length of stay	3.1 (3.4)	5.5 (8.2)

NICU length of stay by GCS		
Mild	3.0 (3.1)	5.5 (6.7)
Moderate	3.2 (3.6)	7.8 (9.8)
Severe	3.4 (4.3)	5.3 (8.4)
Hospital length of stay	8 (16)	16 (22)
Hospital length of stay by GCS		
Mild	7.3 (10)	15.8 (20)
Moderate	15.3 (41.7)	25.5 (29.9)
Severe	9.4 (13)	14.5 (20.9)
Discharge disposition category		
Expired	162 (6.8%)	230 (37%)
Home	1,494 (63%)	144 (23%)
Hospice	1 (<0.1%)	4 (0.6%)
Other	151 (6.3%)	47 (7.6%)
Rehabilitation	224 (9.4%)	120 (19%)
Skilled Nursing Facility	348 (15%)	73 (12%)

[1]Statistics presented: Mean (SD); n (%)

Note. GCS=Glasgow coma scale; ICP=intracranial pressure; NICU= Neurosurgical intensive care unit.

Table 4.2

Characteristics of Traumatic Brain Injury Patients with Automated Pupillometer Assessment and Discharge Disposition

	Discharge Disposition	
Characteristic	Good N = 264[1]	Poor, N = 307[1]
Age	45 (18)	63 (21)
Female	48.8 (17.7)	68.4 (17.9)
Male	43.6 (17.9)	59.7 (21.3)
Sex		
Female	64 (24%)	104 (34%)
Male	200 (76%)	203 (66%)
Race		
White	205 (78%)	231 (75%)
Black or African American	19 (7.2%)	15 (4.9%)
Asian	17 (6.4%)	30 (9.8%)
Native American or Alaska Native	13 (4.9%)	7 (2.3%)
Native Hawaiian or Other Pacific Islander	3 (1.1%)	1 (0.3%)
Unknown	7 (2.7%)	23 (7.5%)
Ethnicity		
Not Hispanic or Latino	211 (80%)	255 (83%)
Hispanic or Latino	42 (16%)	22 (7.2%)
Not Hispanic	1 (0.4%)	1 (0.3%)
Unknown	10 (3.8%)	29 (9.4%)
Mean NPi		
Normal	228 (87%)	149 (49%)
Abnormal	35 (13%)	153 (51%)
Mean NPi by GCS		
Mild	4.0 (1.0)	3.9 (1.1)
Moderate	4.1 (0.6)	3.5 (1.1)
Severe	3.9 (0.9)	2.0 (1.8)
Mean CV		
Normal	170 (70%)	109 (50%)
Abnormal	72 (30%)	109 (50%)
Mean CV by GCS		
Mild	1.5 (0.8)	1.4 (0.7)
Moderate	1.2 (0.5)	1.2 (0.8)
Severe	1.2 (0.6)	0.8 (0.6)
ICP Monitoring		
No	181 (69%)	241 (79%)

Yes	83 (31%)	66 (21%)
Mechanical Ventilation		
No	53 (20%)	38 (12%)
Yes	211 (80%)	269 (88%)
NICU length of stay	5.7 (5.9)	5.0 (6.4)
NICU length of stay by GCS		
Mild	4.9 (6.4)	6.2 (7.1)
Moderate	7.8 (6.5)	8.3 (13.1)
Severe	5.6 (5.5)	4.3 (4.9)
Hospital length of stay	19 (17)	12 (20)
Hospital length of stay by GCS		
Mild	12.8 (13.7)	17.3 (19.9)
Moderate	24.6 (26.0)	28.0 (35.1)
Severe	19.9 (16.5)	9.0 (16.4)

[1]Statistics presented: Mean (SD); n (%)

Note. NPi= Neurological pupillary index; CV= constriction velocity; GCS=Glasgow coma scale; ICP=intracranial pressure; NICU= Neurosurgical intensive care unit.

Table 4.3

Association between First Neurological Pupil Index, First Constriction velocity, and Discharge Disposition

	First NPi			First CV		
Characteristic	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
First NPi/CV						
Normal	4.75	3.05, 7.53	**<0.001**	1.96	1.23, 3.15	**0.005**
Abnormal	Ref	Ref		Ref	Ref	
Age	0.95	0.93, 0.96	<0.001	0.94	0.93, 0.95	<0.001
Sex						
Male	1.18	0.76, 1.83	0.5	1.14	0.70, 1.83	0.6
Female	Ref	Ref		Ref	Ref	
Glasgow Coma Scale						
Mild	Ref	Ref		Ref	Ref	
Moderate	1.18	0.50, 2.78	0.7	0.87	0.36, 2.11	0.8
Severe	0.72	0.38, 1.36	0.3	0.74	0.38, 1.45	0.4
ICP monitoring						
Yes	0.81	0.49, 1.34	0.4	0.87	0.50, 1.51	0.6
No	Ref	Ref		Ref	Ref	
Mechanical ventilation						
Yes	0.45	0.22, 0.89	0.023	0.53	0.25, 1.11	0.094
No	Ref	Ref		Ref	Ref	
NICU length of stay	0.98	0.94, 1.01	0.2	0.95	0.90, 0.99	0.019
Hospital length of stay	1.01	1.00, 1.02	0.2	1.01	1.00, 1.03	0.12

[1]OR = Odds Ratio, CI = Confidence Interval

Note. NPi= Neurological pupillary index; CV= constriction velocity; ICP=intracranial pressure; NICU= Neurosurgical intensive care unit.

Table 4.4

Association between the mean NPi, the mean CV, and discharge disposition

	Mean NPi			Mean CV		
Characteristic	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Mean NPI/CV						
Normal	9.35	5.62, 16.0	<0.001	2.23	1.41, 3.56	<0.001
Abnormal	Ref.	Ref.		Ref.	Ref.	
Age	0.94	0.93, 0.95	<0.001	0.94	0.93, 0.95	<0.001
Sex						
Male	1.16	0.73, 1.84	0.5	1.1	0.68, 1.77	0.7
Female	Ref.	Ref.		Ref.	Ref.	
Glasgow Coma Scale						
Mild	Ref.	Ref.		Ref.	Ref.	
Moderate	1.18	0.43, 2.35	>0.9	0.87	0.36, 2.10	0.8
Severe	0.82	0.42, 1.59	0.6	0.75	0.38, 1.46	0.4
ICP monitoring						
Yes	0.78	0.46, 1.31	0.4	0.8	0.46, 1.39	0.4
No	Ref.	Ref.		Ref.	Ref.	
Mechanical ventilation						
Yes	0.49	0.24, 0.99	0.047	0.55	0.26, 1.14	0.11
No	Ref.	Ref.		Ref.	Ref.	
NICU length of stay	0.98	0.95, 1.02	0.4	0.94	0.90, 0.99	0.02
Hospital length of stay	1.01	0.99, 1.02	0.3	1.01	1.00, 1.02	0.2

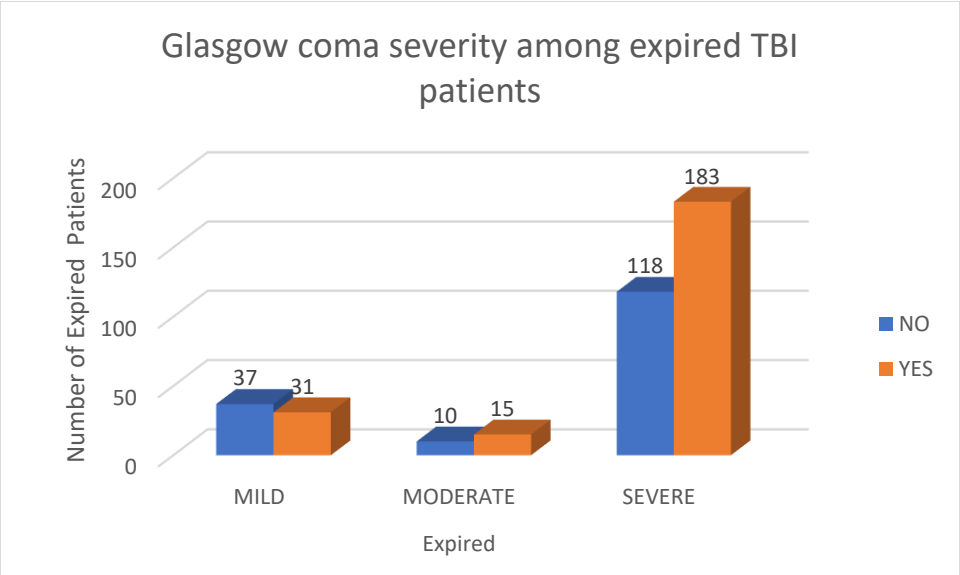
[1]OR = Odds Ratio, CI = Confidence Interval

Note. NPi= Neurological pupillary index; CV= constriction velocity; ICP=intracranial pressure;

NICU= Neurosurgical intensive care unit.

Figure 4.1

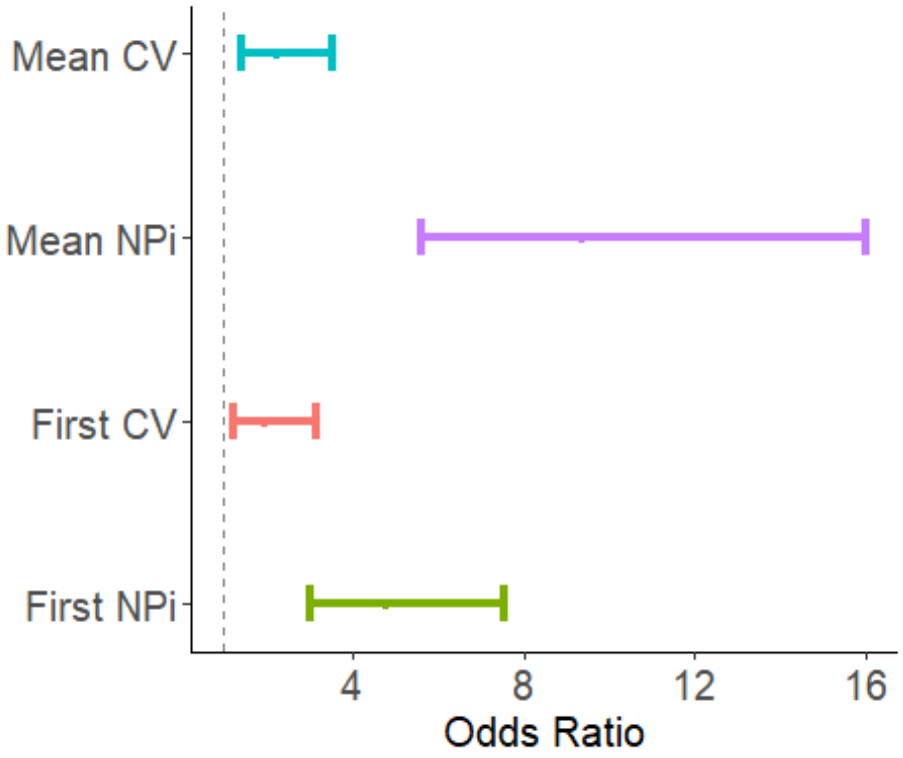
Expired Patients with and without Automated Pupillometer Assessment According to the Glasgow Coma Scale



Note. This figure demonstrates data from one of the unfavorable outcomes (expired) among the TBI patients with and without automated pupillometer assessment. TBI= Traumatic Brain Injury.

Figure 4.2

Forest Plots of Associations Between Neurological Pupil Index, Constriction Velocity, and Discharge Disposition



Note. This figure summarizes the associations between CV, NPi, and discharge disposition

NPi=Neurological Pupil Index, CV=Constriction Velocity

Table 5.4

Relationship between Neurological Pupillary Index and Constriction Velocity

Characteristic	OR[1]	95% CI[1]	p-value
Mean CV	6.99	4.44, 11.2	<0.001

[1]OR = Odds Ratio, CI = Confidence Interval

Note. A patient that has a normal mean are 6.99 times more likely to have a normal NPi

CV= Constriction velocity, NPi= Neurological Pupillary Index