Process of Care and Outcome of Critically Ill Patients with Traumatic Brain Injury

By

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A thesis submitted in conformity with the requirements

for the degree of Doctor of Philosophy in Clinical Epidemiology

Institute of Health Policy, Management, and Evaluation

University of Toronto

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2014

ABSTRACT

This thesis used clinical epidemiology methods to examine the relationship between process of care and outcome of critically ill patients with traumatic brain injury (TBI). First, I evaluated the association between intracranial pressure (ICP) monitoring use and mortality after severe TBI at the patient-level and at the hospital-level. ICP monitoring use was associated with lower mortality at the patient-level [adjusted odds ratio (OR) was 0.44; 95% confidence interval (CI): 0.31-0.63] and at the hospital-level (adjusted OR for death in the quartile of hospitals with highest use compared to the lowest was 0.52; 95% CI: 0.35-0.78). The main implication is that wider utilization of ICP monitoring in managing severe TBI appears warranted pending further studies. Second, I evaluated whether decompressive craniectomy or barbiturate coma provides better value, in terms of health effects and costs, for the management of refractory intracranial hypertension following TBI. Decompressive craniectomy resulted in greater quality-adjusted life expectancy relative to barbiturate coma [average gain was 1.5 quality-adjusted life years (QALYs)] but at higher costs (incremental cost-effectiveness ratio was

$9,565/QALY gained). The main implication is that decompressive craniectomy, for this indication, is a more attractive strategy relative to barbiturate coma at commonly accepted willingness-to-pay thresholds. Third, I examined the relationship between tracheostomy timing and outcomes of TBI patients. Early tracheostomy (≤8 days) was associated with fewer mechanical ventilation days (rate ratio 0.70; 95% CI: 0.66-0.75), shorter ICU stay (rate ratio 0.70; 95% CI: 0.66-0.75), shorter hospital stay (rate ratio 0.80; 95% CI: 0.74-0.86), but not mortality (OR 1.25, 95% CI: 0.80-1.96). The main implication is that clinicians may consider performing early tracheostomy among TBI patients as a mechanism to reduce certain components of in-hospital morbidity but not mortality.

Overall, the studies comprising this thesis have demonstrated how multiple health services research methods and analytical approaches can be used to understand the relationship between processes of care and outcome of patients with TBI.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and sincere appreciation to the following:

First and foremost, to Avery Nathens, my thesis supervisor, for being my role model and mentor, for providing me with endless opportunities, for fostering my personal and professional growth, for being a fierce protector of my interests, and for telling me the truth when I most need it. Without his limitless support, this work would never have been accomplished.

To Robert Fowler and Damon Scales, for advancing my critical thinking skills, for helping me make the best choices, and for providing me with sound advice and new ideas.

To Todd Mainprize, Alexander Kiss and Joel Ray for their incredible help and guidance throughout the different stages of my thesis.

To David Naimark and Murray Krahn, for providing me with reliable and patient explanations to my questions, and helping me overcome challenging parts of my thesis.

To Sharon Dell, Ahmed Bayoumi, Amber Gertzbein, Jennifer James and Errin Barker for their guidance and support in all matters related to the Clinical Epidemiology Program.

And, to the Clinical Epidemiology Program at the Institute of Health Policy, Management, and Evaluation.

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CHAPTER 1: Introduction to Process of Care for Critically Ill Patients with Traumatic Brain Injury

The purpose of this chapter is to:

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2. Provide an overview of the epidemiology of traumatic brain injury and highlight its overall burden.
3. Describe processes of care in the intensive care unit for traumatic brain injury patients.
4. Review previous studies of the relationship between processes of care and outcome among critically ill traumatic brain injury patients.
5. Describe a conceptual framework for studying the relationship between processes of care and outcome among critically ill traumatic brain injury patients.
6. Introduce the general objectives of the thesis.

Overview of Human Brain Structure and Function

The human brain comprises neurons, glial cells, and blood vessels. Recent estimates have shown that the average adult brain contains more than 80 billion neurons and a similar number of glial cells.[1] The telencephalon (cerebral hemispheres)

constitutes the largest part of the brain and is mounted on other brain structures.[2] Other anatomical divisions of the brain are located caudally and include the diencephalon (thalamus, hypothalamus, and pituitary gland), the mesencephalon (tegmentum and superior and inferior colliculi), and the rhombencephalon (cerebellum, pons, and medulla oblongata).[2]

The outer layer of the telencephalon, the cerebral cortex, is the most likely area in the brain to be damaged by traumatic brain injury (TBI).[2] The cerebral cortex is a 2 to 4 millimeter thick sheet of neural tissue with a convoluted topography.[3] When unfolded, it has a total surface area of approximately 2400 square centimeters.[4] Each cortical ridge is called a gyrus, and each groove separating two gyri is called a sulcus. The cortex is referred to as the grey matter because it consists of neural cell bodies and capillaries and contrasts with the underlying white matter, which consists mainly of myelinated sheaths of neuronal axons.[3] The phylogenetically newest portion of the cerebral cortex (i.e., the neocortex) is composed of six horizontal layers of neurons, segregated mainly by cellular type and neuronal connections, whereas the more ancient part of the cerebral cortex (i.e. the hippocampus) has at most three layers.[3] The neocortex can be further divided into 52 regions known as Brodmann areas[5], each distinguished by a unique cytoarchitecture.[3]

The cerebral cortex of each hemisphere is divided anatomically into six major lobes.[6,7] The frontal lobe is located under the forehead and its functions include abstract thinking, attention, behavior, and problem solving tasks.[8] Near the back and

top of the head is the parietal lobe, which contains areas involved in somatosensation, hearing, language, attention, and spatial cognition.[8] The temporal lobe, which is located just above the ear, controls the auditory and visual memories and is involved in language, hearing, and speech.[8] At the back of the head is the smallest lobe, the occipital lobe, whose main functions include visual reception, visual-spatial processing, and color recognition.[8] The limbic lobe is an arch-shaped region of the medial surface of each cerebral hemisphere that has a role in emotional behavior and memory.[8] The insular lobe (or insular cortex) is a portion of the cerebral cortex folded deep in the lateral sulcus, which is a fissure separating the temporal lobe from the frontal and parietal lobes.[7] The insular lobe is believed to be involved in consciousness, emotions and the regulation of the body's homeostasis.[9-11] Although the division of the cerebral cortex into lobes is helpful for reference, current evidence suggests that these do not function independently, and research has been directed toward exploring the functional inter-dependence among the six lobes.[2]

The cerebral cortex can also be divided into three functional divisions: sensory areas, motor areas, and association areas.[3] The sensory areas receive signals from the sensory nerves by way of relay nuclei in the thalamus and include areas in the occipital (visual area), temporal (auditory area), and parietal lobes (somatosensory area).[3] The motor areas, located in the posterior portion of the frontal lobe, projects axons down to the motor neurons in the brainstem and spinal cord.[3] Association areas occupy the remaining parts of the cerebral cortex and are involved in multiple

complex processes including the integration of sensory information with memories, perception, language, abstract thinking, and decision-making.[12]

Although the brain represents only 2-3% of the total body weight, it has the highest metabolic activity of all organs.[13] In the waking state, the brain receives approximately 15% of the cardiac output and normally consumes 20% of the body's oxygen supply and up to 50% of its glucose supply.[13,14] Under normal conditions, 95% of the energy requirements of the brain are derived from aerobic glycolysis.[15] Although the brain relies almost exclusively on blood glucose as its energy source, it has low stores of glucose in the form of astrocyte glycogen, in contrast to other parts of the body, such as the skeletal muscles and the liver.[16] Therefore, hypoglycemia can result in a rapid deterioration in global cerebral function and loss of consciousness.[14] Notable exceptions include prolonged fasting and exercise, in which the brain may temporarily use ketone bodies and lactate as alternative energy substrates.[14,17] However, even though the oxidation of ketone bodies may meet up to 75% of total cerebral energy demand, it is unable to completely replace glucose as cellular fuel.[18]

The cerebral blood flow is tightly regulated to provide an adequate supply of primary metabolic substrates, oxygen and glucose, to the brain. This process, termed autoregulation, is accomplished mainly by changes in the diameter of cerebral arterioles.[19] Although the underlying physiology of the cerebral autoregulation process is not completely understood, a number of mechanisms that mediate the cerebral vascular tone in response to certain stimuli have been

proposed, including the release of endothelial-derived vasoactive substance, the activation of potassium channels in vascular smooth muscles, and pressure-mediated myogenic responses.[20] The autoregulation process responds to changes in metabolic demand (increased demand causes vasodilation), blood pressure (low blood pressure causes vasodilation), blood viscosity (reduced viscosity causes vasoconstriction), arterial partial pressure of carbon dioxide (low carbon dioxide causes vasoconstriction), and arterial partial pressure of oxygen (hypoxia causes vasodilation).[15,20]

Definition of Traumatic Brain Injury

Despite being protected by the thick bones of the skull, suspended in the cerebrospinal fluid, and isolated from the bloodstream by the blood-brain barrier, the human brain is susceptible to damage from a variety of conditions, including traumatic injuries. The definition of traumatic brain injury (TBI) remains debatable. In response to the lack of a universal operational definition for TBI, the Centers for Disease Control and Prevention published a standard clinical case definition of TBI in 1995. They defined TBI as "an occurrence of injury to the head (arising from blunt or penetrating trauma or from acceleration-deceleration forces) that is associated with symptoms or signs attributable to the injury: decreased level of consciousness, amnesia, other neurological or neuropsychological abnormalities, skull fracture, diagnosed intracranial lesions, or death".[21] However, the above definition does not encompass other distinct forms of TBI, e.g., blast-induced TBI. To overcome this

limitation, Maas et al. recently proposed a more comprehensive definition for TBI: "brain damage resulting from external forces, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (e.g., gunshot) or blast waves from an explosion. The nature, intensity, direction, and duration of these forces determine the pattern and extent of damage".[22] The term 'head injury' is sometimes used interchangeably with TBI. However, it is a broader descriptor that includes injuries to the face and scalp, e.g., lacerations and abrasions, which may be present without underlying brain damage. In this thesis, I avoid the use of this term.

The clinical manifestations of TBI range from asymptomatic presentation, or subtle transient behavioral and/or neurophysiological changes in its mildest form, to coma and death for the most severe injuries. In practice, the confusion in the definition of TBI pertains mainly to the mild end of the TBI spectrum, as considerable heterogeneity remains in the definition of mild TBI among different studies.[23] Throughout this thesis, I focus on the other end of the TBI spectrum: severe TBIs that require management in the intensive care unit.

Classification of Traumatic Brain Injury

TBI can be classified using different approaches. One approach is to classify TBI based on the mechanism of injury: blunt (cranial contents have not been penetrated), penetrating (skull is penetrated and brain is exposed to air), and blast TBIs (brain damage due to blast waves from an explosion).[22] This approach is

helpful from an epidemiologic perspective because it divides TBIs into more homogenous entities; each has a different natural history.[22]

In clinical practice, scoring systems are commonly used to classify the severity of injury based on the degree of depression of the level of consciousness. The Glasgow Coma Scale (GCS) is the most commonly used clinical scoring system for TBI severity (Table 1.1).[22,24] The GCS consists of three scales (eye, verbal, and motor scales), each assessing a different aspect of reactivity.[24] The motor component provides more discrimination in patients with severe injuries, while the eye and verbal components are more helpful among patients with milder injuries.[23] For the purpose of classification, the sum score of the three components is used. Severe TBI is defined as a GCS score of 3-8, moderate TBI as a GCS score of 9-13, and mild TBI as a GCS score of 14-15.[23] The main limitation of the clinical classification system is the potential confounding by medication-induced sedation, neuromuscular blockade, and intoxication.[25]

Contrary to clinical classification, the classification of TBIs based on structural damage using neuroimaging is not influenced by these confounders.[22] In 1991, Marshall et al. proposed a descriptive classification system based on the presence or absence of a mass lesion and/or signs of diffuse brain swelling in computerized tomography images (Table 1.2).[26] However, the Marshall classification has important limitations, such as the broad differentiation of diffuse injuries and mass lesions and the lack of specification of the type of mass lesions (e.g., epidural versus subdural hematoma). Better discrimination among brain injuries, especially for the

purpose of prognosis, has been demonstrated when more individual computerized tomography findings are specified.[27]

TBI can be isolated, or it can be associated with extracranial injuries in approximately 35% of cases.[28] Severe extracranial injuries can exacerbate brain damage as a result of hypotension, hypoxia, or coagulopathy.[23,28] Therefore, it is highly relevant to report the severity of these injuries in addition to the severity of TBI. Extracranial injuries are commonly scored using the Abbreviated Injury Scale (AIS; Table 1.3).[29] The AIS is an anatomically based coding system that specifies the following: the injured body region, the specific anatomical structure injured, and the type and the severity of injury. The severity part of the AIS code is on a scale of one (minor, e.g., superficial laceration) to six (unsurvivable, e.g., crush injury of the brain stem).[29]

In this thesis, I study severe blunt TBIs, defined using the GCS clinical scoring system. Using the AIS, I focus on patients with isolated TBI who have no other significant injuries, with detailed examination of individual intracranial injuries (Table 1.4).

Pathophysiology of Traumatic Brain Injury

Traumatic injuries to the brain range from no visible abnormalities in the case of minor TBI to superficial bruising (contusion) and, in severe cases, profound brain

swelling (edema), large collections of blood (hematomas), and/or diffuse shearing of white matter axons (diffuse axonal injury).

TBI is not a single pathophysiological event but a complex dynamic disease process.[30] The pathophysiology of brain damage after traumatic injury can be divided into two general processes: primary and secondary. The primary injury is the tissue deformation that damages the neurons, glia and blood vessels at the moment of impact and cannot be modified by medical intervention, other than trauma prevention programs. However, the severity of the primary injury can be described and quantified for prognostic purposes. The primary injury initiates a cascade of intracellular and extracellular processes that mediate the more delayed phase of secondary injury, which evolves over the minutes, hours, days, and even weeks following the initial injury.[31-33] During this phase, the brain is exquisitely sensitive to further damage from superimposed secondary insults. Secondary insults, which are "second hits" that occur after injury such as systemic hypotension, hypoxia, hypocapnia, pyrexia, and seizures, need to be distinguished from secondary injuries, which are processes that develop after the unavoidable primary injury as the result of a biochemical cascade initiated by the trauma.[31,34] The secondary insults can further exacerbate brain damage and can have a profound negative effect on the patients' long-term outcome.[31] The main focus of early medical and surgical intervention for patients with TBI is the prevention of secondary insults.[35-40]

Secondary Injury Processes

The concept of delayed secondary injury is supported by the observation of the lucid interval in severe TBI patients.[34] Approximately one third of severe TBI patients who die demonstrate a period of lucidity sufficient to obey commands or speak.[41,42] This period implies that the primary injury was not severe enough to cause death, which emphasizes the importance of delayed secondary injury processes.[34] Furthermore, these secondary injury processes make the injured brain extremely vulnerable to superimposed secondary insults, which would have been well tolerated under normal conditions prior to injury. The principle mechanisms of secondary injury include hypoxia-ischemia, edema, excitotoxicity, calcium dysregulation, apoptosis, metabolic and mitochondrial derangement, oxidative stress, inflammation, and defective cerebrovascular autoregulation.[34] These deleterious mechanisms are synergistic, interrelated, and work in parallel and/or sequential cascades.[34]

The incidence of hypoxic-ischemic brain damage observed in autopsies of TBI patients ranges between 60 to 90%.[34,42] The ischemic changes could be global due to low cerebral perfusion pressure (CPP) or high intracranial pressure (ICP), or focal to areas inside and around mass lesions that may impair local cerebral blood flow (e.g., hematomas and contusions).[34] Damage to a parent vessel (e.g. the internal carotid artery) can also lead to focal ischemia in areas of vulnerable parenchyma.

Post-traumatic brain edema is common following TBI, especially among patients with severe injuries.[43] This type of edema was shown to be mainly cytotoxic (edema due to dysfunction of cellular membrane ionic pumps leading to cellular retention of

water and sodium) rather than vasogenic (edema due to the breakdown of the blood-brain barrier with protein extravasation into the parenchymal extracellular space).[44] The development of brain edema is a primary contributor to intracranial hypertension. The elevation in ICP impedes the cerebral blood flow and initiates a vicious cycle of ischemia leading to more cytotoxic edema and further increase in ICP.[34]

Following TBI, the presynaptic nerve terminals and astrocytes release excessive amounts of excitatory neurotransmitters, such as glutamate and aspartate, into the extracellular space in a process termed excitotoxicity.[34] These neurotransmitters bind to postsynaptic receptors and thereby activate ion channels, leading to a rise in intracellular calcium and sodium levels.[34] The increase in the level of these intracellular ions passively draws water and chloride into the intracellular compartment. The resultant cellular swelling and high calcium concentration cause increased mitochondrial membrane permeability, mitochondrial dysfunction, organelle swelling, necrosis, apoptosis, and the release of proteolytic enzymes.[34,45] These processes result in the further propagation of delayed neuronal injury and death following TBI.

After TBI, the brain attempts to restore ionic homeostasis by the reuptake of neurotransmitters and ionic pumping.[34] These processes are energy dependent and lead to an abrupt surge in glucose utilization by the injured brain. Previous studies have shown that the increase in glucose utilization is maximal in viable areas of the brain surrounding mass lesions and may last up to 5-7 days.[46] However, the normal

oxidative metabolism process in the injured brain is compromised because of inadequate cerebral blood flow, cerebral hypoxia, and/or mitochondrial failure.[15] Therefore, cells shift towards anaerobic glycolytic pathways to meet their increased energy demand.[15]

Reactive oxygen species are important contributors to secondary brain damage.[47] In fact, many secondary injury processes, such as mitochondrial dysfunction and elevated intracellular calcium levels, generate free radicals, and in turn, free radicals trigger and perpetuate many other secondary injury processes.[34,47] The brain is particularly vulnerable to free radicals because it contains high concentrations of polyunsaturated fatty acids, which are easily damaged by oxidative stress.[34,48]

Polymorphonuclear leukocytes start to accumulate in the injured parts of the brain within 24 hours of the initial injury, followed by macrophages and lymphocytes after 36-48 hours.[34,49,50] These inflammatory cells secrete a wide variety of bioactive substances including cytokines.[34] Cytokines are vasoactive substances that increase vascular permeability and, therefore, may increase ICP by worsening brain edema.[34] They also have direct cytotoxic effects on neurons and glial cells.[34,51]

Following a severe primary injury, the cerebral autoregulation process is often disrupted, but there is variability in the location, magnitude, and duration of this disturbance.[15] In addition, derangement may affect different mechanisms of cerebrovascular autoregulation. Typically, carbon dioxide reactivity is mostly preserved while other mechanisms are affected.[15] Hyperemia, defined as increased cerebral blood flow in excess of the cerebral metabolic demands, has been

demonstrated in up to 55% of severe TBI patients especially between 1 and 5 days following the primary injury.[15,52,53] Autoregulation in response to changes in blood pressure and viscosity can also become defective within the first few days following severe TBI in some patients.[54,55] The exact underlying mechanism of defective autoregulation after TBI is not clear.[15] However, endothelial damage due to oxygen free radicals following TBI has been proposed as the etiology responsible for the perpetuation of defective cerebrovascular autoregulation.[56,57] The impact of TBI on cerebral autoregulation in response to hypoxia is less clear. Animal models have suggested that severe TBI might impair the normal vasodilatation response to hypoxia, such that hypoxia actually results in an actual decrease in cerebral blood flow.[58]

The defective autoregulation processes are critical mechanisms for the development of local and diffuse cerebral swelling, and elevated ICP.[15] Furthermore, the status of the cerebrovascular autoregulatory mechanisms determines the impact of the therapeutic interventions that manipulate ICP or CPP. For example, reduced CPP because of hypotension or high ICP normally results in a compensatory vasodilation to maintain constant blood flow, but when autoregulation is defective, low CPP may lead to critically low levels of cerebral blood flow and consequently brain ischemia.[15] Although low blood viscosity normally causes vasoconstriction and thereby lowers the cerebral blood volume and ICP, medical interventions that reduce blood viscosity (e.g. mannitol) do not induce a vascular response in the context of impaired viscosity-related autoregulation, such that the ICP does not significantly change.[15]

Elevated ICP is a common pathway for multiple secondary injury processes as described above. The underlying conditions that mediate high ICP following severe TBI include increased cerebrospinal fluid volume, increased cerebral blood volume, cytotoxic edema, and blood-brain barrier damage associated with vasogenic edema.[15] Resistance to cerebrospinal fluid absorption, increased cerebral blood volume, and cytotoxic edema account for the vast majority of ICP elevations following severe TBI.[59]

The pressure-volume relationship between ICP and the volume of intracranial contents (blood, cerebrospinal fluid and brain tissue) can be explained by the Monro-Kellie hypothesis.[60-62] The hypothesis states that the total volume is constant, and any increase in the volume of any of the contents must be accompanied by an equal decrease in other components to maintain a constant ICP.[62] Most of the compensation comes from the translocation of cerebrospinal fluid and venous blood but, at a certain point, this buffering mechanism is exhausted and ICP starts to rise exponentially even with little increase in volume.[15] ICP higher than 20 mm Hg is a significant independent determinant of death and long-term disability.[63] ICP of 20-40 mm Hg increases the odds of mortality by 3.5-fold; ICP above 40 mmm Hg increases the same odds ratio by 6.9-fold, and ICP elevations that are refractory to treatment are associated with an odds ratio for mortality of 114.3.[64]

'Superimposed' Secondary Insults

Any condition that impairs the cerebral energy metabolism can be considered a potential secondary insult following acute TBI. Secondary insults may further damage the brain and can have a profound negative effect on TBI patients' risk of death and long-term disability. These 'second hits' can be divided into two categories: insults that decrease the delivery of cerebral energy substrates (e.g., hypotension, hypoxia, hypoglycemia, and anemia) and insults that increase the cerebral energy demands (e.g., fever and seizures).[65] Although the occurrence of these secondary insults would be well tolerated by a normal brain, the defective compensatory mechanisms due to the previously described ongoing secondary injury processes make the injured brain exquisitely sensitive to those second hits.

Multiple studies have demonstrated that the occurrence of hypotension following TBI strongly correlates with poor neurological recovery.[31,66] A single episode of hypotension following acute TBI doubles the odds of mortality.[31,67] When the number of hypotensive episodes increases from 1 to 2 or more, the odds ratio for death increases from 2.1 to 8.1.[67] The negative impact of hypotension on patients' outcome is consistent regardless of whether the hypotensive episode occurs early during the resuscitation period or later during the patient's stay in the intensive care unit.[66]

Hypoxia is another secondary insult that can be associated with a poor neurological outcome.[68] Although the negative effect of hypoxia on the injured brain is not as strong as the effect of hypotension, the severity and duration of in-hospital oxygen desaturation are both independent predictors of mortality and poor recovery.[69,70]

The effects of hypoxia are not limited to the decreased supply of energy substrate, but it may also involve cerebral vasodilatation, if autoregulation is intact, and consequently high ICP.[65] Pulmonary complications that can result in hypoxia are common following TBI. Upon arrival at the hospital, early hypoxia can be due to hypoventilation, airway obstruction, aspiration, hemothorax, or pneumothorax.[65] Hypoxia that develops later can be due to a lung contusion, atelectasis, pneumonia, adult respiratory distress syndrome, or pulmonary emboli.[65]

Anemia can have detrimental consequences on the injured brain because hemoglobin-bound oxygen is crucial to meet cerebral metabolic demands.[15] Additionally, the compensatory increase in cerebral blood flow with anemia after TBI can increase ICP.[65] Although an ideal target for the hemoglobin level in TBI remains unknown, anemia on admission strongly correlates with worse long-term clinical outcomes following TBI.[71]

Several studies have suggested that fever after TBI is another potential source of further injury and can be associated with higher mortality and poor recovery.[69,72-76] For each degree Celsius elevation in body temperature, the cerebral metabolism increases by 10-13%, and in the context of intact autoregulation, the cerebral blood flow (and volume) increases to meet the higher metabolic demands.[15,74] The resulting increase in cerebral blood volume may lead to higher ICP in TBI patients.[77,78] Among patients with impaired metabolic autoregulation, the cerebral blood flow may not increase proportionally in response to fever and the resultant

higher metabolic demands, which may further exacerbate the metabolic crisis of the injured brain.[15]

Although there is not a clear relationship between the occurrence of early seizures and a worse neurological outcome, seizures can dramatically increase the cerebral metabolic rate and oxygen consumption.[65,79] If the metabolic autoregulation of the cerebral blood flow is defective, such changes may exacerbate the ischemic changes of the injured brain. An increase in the extracellular glutamate level has also been reported following seizures in severe TBI patients, which may reflect enhanced excitotoxicity and worsening cellular crisis.[80]

Epidemiology of Traumatic Brain Injury

Definitions

Epidemiology is defined as the study of the patterns, causes, and effects of health-related states or events in defined populations.[81] It involves the application of epidemiological knowledge and methods to promote, protect and restore health.[81] In the field of TBI, knowledge of epidemiology is critical to plan and evaluate preventive strategies and to guide the management of patients who have already sustained injuries.[23]

The prevalence of TBI is the proportion of TBI cases in a specific population at a given point in time.[23] This measure includes all people living with the long-term

consequences of TBI, such as physical or mental impairments, disabilities, or complaints, together with all new TBI cases.[23]

The incidence of TBI is a measure of the risk of TBI occurrence within a specified period of time.[23] It is typically expressed as a proportion or a rate, with the denominator being 100,000 people at risk.[23]

The TBI mortality rate is a measure of the number of deaths due to TBI in a specific population, scaled to the size of that population, per unit of time.[81] It is typically expressed in units of deaths per 1000 people per year (e.g., a mortality rate of 9.5 in a population of 100,000 equals 950 deaths every year in that population).[23] The TBI case fatality rate is defined as the number of deaths attributable to TBI in relation to the total number of TBI patients.[23]

In this section, the unfortunately incomplete epidemiology of TBI is summarized. As discussed before, inconsistency in the definition and classification of TBIs has made the epidemiology of TBI difficult to describe and compare across different populations, and even within the same population over time. This problem pertains mainly to mild TBIs, which represent approximately 80-90% of all TBIs.[82,83] Patients who sustain mild TBI may not seek medical attention and therefore cannot be easily quantified. Another confounding factor is the variability in the inclusion criteria for mild TBI among epidemiologic studies.[23] In addition, radiological imaging can only capture momentary snapshots of the dynamic process of TBI. Neuroimaging for suspected TBI can be initially classified as normal, but as TBI evolves, it may show evidence of a pathological process if repeated at a later time point.[22] Because of

these methodological shortcomings in the epidemiology of TBI, the epidemiologic data reported in TBI literature should be interpreted with great caution.

Burden of Traumatic Brain Injury

TBI is a public health and socioeconomic problem with major consequences. It presents a multidimensional challenge of growing magnitude worldwide. According to the World Health Organization, TBI will surpass many other diseases as the third leading cause of global mortality and disability by 2020.[84] Globally, more than 10 million people every year suffer TBIs serious enough to result in death or hospitalization, and an estimated 57 million people currently alive have been hospitalized with one or more TBIs.[85]

In the United States alone, an estimated 1.7 million TBIs occur either in isolation or alongside other injuries annually.[86] As a result of these injuries, 1.37 million people visit the emergency department; 275,000 people are hospitalized; and more than 53,000 individuals die, representing one third of all injury-related deaths.[86] Moreover, a considerable proportion of TBI survivors incur temporary or permanent disability. According to the Centers for Disease Control and Prevention, the estimated prevalence of TBI in the United States is approximately 5.3 million, which represents approximately 2% of the total population.[85] The true prevalence is likely higher because this estimate does not include patients who recovered from TBI without a long-term disability or who were never treated.[85]

The estimated annual burden of TBI on the United States economy is more than $75 billion, with the costs for disability and lost productivity outweighing the costs for acute medical care.[87] However, this calculation is likely an underestimate of the actual cost, as it does not include the indirect effects of TBI on the patients' families and other caregivers.[23]

The majority of TBI patients present with mild injuries.[82] Severe TBI, although it represents approximately 10% of all TBIs, contributes the greatest proportion of death, disability and costs related to TBI.[82,87,88]

Incidence

There is a large variation in the reported incidence rates among different epidemiological studies, even within the same population.[89] This variation is likely due to variation in the definition of TBI, different inclusion criteria, sampling errors, and actual differences.[23]

According to the Centers for Disease Control and Prevention, the approximate annual incidence of TBI in the United States, between 2002-2006, was 579 per 100,000.[86] This estimate does not include TBI cases that did not present to the emergency department. The incidence of TBI-related hospitalizations, including in-hospital deaths, was 111 per 100,000 population.[86]

Overall, approximately 1.4 times as many TBIs occur among males as among females.[86] However, the male preponderance gradually decreases among individuals

younger than 20 years and older than 60 years until there is no clear gender difference.[90]

A trimodal age-specific TBI incidence has been reported by multiple studies.[82] The incidence peaks in early childhood (aged 0-4 years), late adolescence/early adulthood (aged 15-19 years), and in the elderly (aged 75 years and older).[82] In addition, certain groups of the population are at a higher risk for sustaining TBI, such as people detained in penal institutions and military personnel.[91,92]

A consistent increase in the median age of TBI patients over time has been reported by different studies.[22,93,94] This increase in the age of the TBI population is likely due to a combination of factors, including the aging populations of high-income countries. Furthermore, road traffic safety laws and preventive measures have reduced the incidence of TBI due to motor vehicle collisions, which primarily occur among younger people.[23]

Mortality Rates

Because of the variability in data collection and lack of standardization, the TBI mortality data in the literature are widely variable and difficult to compare across different studies.[23] Similarly, studies of temporal trends in TBI mortality are difficult to interpret.

The reported annual TBI mortality rates in the United States, including all prehospital and in-hospital deaths, range between 17.4 and 24.6 per 100,000.[86,95-97] The case fatality rate for TBI in the United States also varies across different studies

due to different methodology, with variability from 4 to 17 deaths per 100 TBI patients.[82,98-100]

On average, 39% of severe TBI patients die from their injuries, and more than one third of survivors remain in a vegetative state or experience long-term severe disabilities.[101]

Cause of Injury

The main causes of TBI are transportation incidents, falls, and gunshot wounds.[23] Worldwide, approximately 60% of TBIs are due to motor vehicle incidents, and 20-30% are due to falls.[102] However, there is considerable variation in the causes of TBI among different populations.[102]

In the United States, falls are currently the leading cause of TBI (35.2%) among all age groups, especially children (50.2% of TBIs among individuals aged 0-14 years) and the elderly (60.7% among individuals aged 65 years or older). Among all age groups, motor vehicle incidents are the second leading cause of TBI (17.3%), but they contribute the largest proportion of TBI-related deaths (31.8%).

Introduction to Process of Care and Outcome

In 1966, Avedis Donabedian, a physician and healthcare researcher at the University of Michigan, developed a conceptual model for evaluating of the quality of health

services.[103] The Donabedian model can be represented by a chain of three interconnected domains: structure, process of care, and outcome.[104]

Structures include all factors that affect the context in which care is delivered.[104] They include the physical facilities, equipment, human resources, and staff qualifications. The processes of care involve the particulars of care that patients actually receive.[104] These processes involve all the actions that make up healthcare, including preventive measures, diagnosis, treatment, rehabilitation, and patient education. Outcomes represent all the effects of healthcare on individual patients or populations, including changes to health status, behavior, patient satisfaction and health-related quality of life.[104]

The focus of this thesis is on examining the relationship between two domains of the Donabedian framework, process of care and outcome, in the population of critically ill TBI patients.

Process of Care for Traumatic Brain Injury in the Intensive Care Unit

Soon after initial resuscitation in the emergency department, patients with severe TBI are typically transferred to and managed in an intensive care unit (ICU) setting. The processes of care for severe TBI patients in the ICU can be divided into two temporal phases: early and late. The two phases differ in terms of goals, and consequently the corresponding processes of care are different.

Early Phase of ICU Care

The main goals of the early phase are anticipation, recognition, and early treatment of secondary insults to the injured, and therefore exquisitely sensitive, brain.[65] These processes are usually delivered within the first few days following admission to the ICU. This phase typically involves close monitoring of a multitude of systemic physiological variables, including hemodynamic parameters, pulse oximetry, temperature, hemoglobin level, blood glucose, electrolyte panel, and fluid intake and output. In addition to monitoring their clinical neurological status, severe TBI patients are often monitored for markers of secondary injury processes. The two processes often monitored are intracranial hypertension and cerebral ischemia.

ICP in severe TBI patients cannot be reliably monitored based on clinical assessment alone.[65] The clinical symptoms of high ICP, such as headache and vomiting, cannot be elicited in comatose patients.[65] Papilledema is rare following severe TBI, even among patients with proven intracranial hypertension.[105] Pupillary dilatation and decerebrate posturing can be late signs of high ICP.[65] Moreover, they may occur in the absence of intracranial hypertension. Certain features in computerized tomography imaging, such as brain swelling and midline shift, can predict raised ICP.[65] However, high ICP can also occur in the absence of these abnormalities. Therefore, continuous ICP monitoring via an invasive tool is believed to be a more reliable means for the early detection of raised ICP, which may facilitate more prompt treatment to control the rising pressure inside the rigid skull. Several types of ICP monitors are available. Among them, ventricular catheters

provide the most accurate and reliable measurements, with the additional advantage of treating raised ICP by the drainage of cerebrospinal fluid as needed.[106] Invasive ICP monitoring is continued for as long as the treatment of intracranial hypertension is required, typically for 3-5 days.[65]

When intracranial hypertension is diagnosed, several measures can be undertaken to control the rising pressure. Initially, lesions amenable to surgery should be ruled out by computerized tomography. In the absence of such lesions, the first-line treatment options include hyperosmolar therapy, normalization of arterial carbon dioxide level, optimal sedation, neuromuscular blockade, and external drainage of cerebrospinal fluid.[35,39,40] When these measures fail, decompressive craniectomy and barbiturate coma are often used as second-tier strategies to treat intracranial hypertension.[107]

As with elevated ICP, there are no reliable clinical features for cerebral ischemia following TBI.[65] The ideal monitoring tool for ischemia would provide continuous information on the global and regional cerebral blood flow.[65] Unfortunately, no such device exists. The available monitoring technologies for cerebral ischemia include monitors that directly measure the cerebral perfusion pressure or the cerebral blood flow or velocity, and monitors that indirectly assess the cerebral blood flow adequacy by monitoring the cerebral tissue oxygenation. Monitoring the cerebral perfusion pressure, calculated by subtracting ICP from the mean arterial blood pressure, represents the simplest and most readily available method to monitor for cerebral ischemia. However, because of the frequently impaired autoregulation of

the injured brain, the cerebral blood flow might be inadequate even in the presence of normal cerebral perfusion pressure values. The cerebral flow velocity can be intermittently measured using transcranial Doppler ultrasound. This technique is mainly helpful to discriminate between hyperemia and vasospasm and may therefore guide management when either condition is suspected.[108] The cerebral blood flow can be measured intermittently, using xenon- or perfusion computerized tomography, or continuously, using invasive probes that utilize thermal diffusion or the laser Doppler flowmetry method.[65] The adequacy of the cerebral blood flow can be assessed indirectly using measures of cerebral tissue oxygenation.[65] These measures can assess global cerebral oxygenation, such as jugular venous oxygen saturation catheters, or regional oxygenation, such as brain tissue oxygenation probes.

The management of suspected cerebral ischemia depends on the underlying cause. In general, the management options involve the administration of a high inspired oxygen fraction and/or augmentation of the systemic blood pressure.

Severe TBI patients often cannot maintain a patent airway because of their reduced level of consciousness and depressed protective reflexes.[109,110] Therefore, another process of care commonly delivered during this phase of ICU care is endotracheal intubation and mechanical ventilation to ensure a secure airway, allow for deep sedation and neuromuscular blockade as needed, and provide an optimal oxygenation and ventilation environment for the injured brain.

Late Phase of ICU Care

Once the risk of secondary brain injury has been adequately addressed, the focus of later processes of ICU care shifts to supportive management, weaning and liberation from life support measures including mechanical ventilation, and mobilization in preparation for transfer to a lower intensity care setting.

At this stage, severe TBI patients often undergo tracheostomy to ensure a patent airway when the level of consciousness remains persistently depressed, and thereby facilitate liberation from mechanical ventilation.[109,111] By providing a conduit for suctioning, tracheostomy can also improve pulmonary toilet, which may further accelerate weaning and liberation from mechanical ventilators, decreasing the risk of pneumonia and other ventilator-associated adverse effects in these patients.[111] In contrast to other critically ill patients, isolated TBI patients often require little or no assistance from mechanical ventilators and may be liberated more promptly from the ventilator once the airway is secured with a tracheostomy.[110,111]

Impaired tone and coordination of swallowing muscles and abnormal cognitive processes critical to normal swallowing are common among severe TBI patients.[112] The abnormal swallowing mechanism puts these patients at high risk for respiratory and nutritional complications. Therefore, patients recovering from severe TBI usually require a comprehensive swallowing assessment prior to resuming oral feeding. Patients with severe swallowing dysfunction or a persistently low level of consciousness may require the placement of a gastrostomy tube at this stage of ICU care to facilitate long-tem tube feeding during the recovery phase. When compared to other methods of enteral feeding, such as nasogastric or

orogastric tube feeding, gastrostomy feeding causes less discomfort by reducing nasopharyngeal irritation and has lower rates of complications, including bleeding tube blockage and dislodgment.[113]

Other issues typically addressed at this stage of ICU care include agitation, dysautonomia, and the definitive management of persistent post-traumatic hydrocephalus.

Processes of ICU Care under Study

In this thesis, I study the relationship between TBI outcome and three processes of ICU care that are delivered at different time points: invasive ICP monitoring, management of refractory intracranial hypertension, and tracheostomy timing.

Previous Studies of Processes of ICU Care and Outcomes Following Traumatic Brain Injury

In this section, I review previous studies that have examined the relationship between the processes of ICU care under study in this thesis and the outcome of TBI patients. I searched MEDLINE database for relevant studies published between January 2000 and December 2012 using the keyword "traumatic brain injury" and the subheadings "intracranial pressure", "decompressive craniectomy", "barbiturate" or "tracheostomy". I also searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews

using the key word “traumatic brain injury”. The search was supplemented by a review of the reference lists of key articles.

The Brain Trauma Foundation first recommended the use of invasive ICP monitoring as part of severe TBI management guidelines in 1995.[114] The recommendation was primarily based on indirect evidence from observational studies that showed a consistent association between raised ICP and worse outcomes following TBI.[63,115-117] Despite its plausible benefit, the effectiveness of invasive ICP monitoring utilization has not been established. Over the last decade, multiple studies have examined the relationship between ICP monitoring use and TBI outcome. Previous studies showed conflicting results (Table 1.5). Although some found an association between the use of ICP monitoring and better outcomes[118-120], others showed higher mortality and worse functional outcome with ICP monitoring use.[121] However, the previous observational studies in this area suffered from a number of limitations. Common methodological shortcomings include small sample size, absent or inadequate adjustment for important confounders, and selection bias.[122,123] Furthermore, none of the previous multicenter cohort studies took into account the hierarchical structure of the data and the clustering of patients’ management and outcomes at different care levels.

The only randomized controlled trial of ICP monitoring compared care focused on maintaining ICP at 20 mm Hg or lower and care based on serial imaging and clinical examination in Latin American hospitals where ICP monitoring is rarely used.[124] The trial showed no significant difference between the two groups in the primary

outcome, a composite measure based on the percentile improvement across 21 measures of functional and cognitive performance.[124] However, the trial was not sufficiently powered to detect a mortality difference between the two management protocols.[124] In addition, although an association between intracranial hypertension and higher mortality is well established, prior studies found no independent association between raised ICP and neuropsychological functioning following TBI.[125] Because 12 of the 21 equally weighted components of the composite measure in this trial were neuropsychological tests, neuropsychological performance is highly influential in the composite endpoint.[126] In light of prior studies, this issue may have increased the risk of type II error in this trial.[126] Furthermore, differences in injury characteristics, prehospital, ICU, and post-ICU structure and processes of care, and the observation of 'late mortality' due to medical complications, accounting for more than one third of deaths following TBI in Latin America, may render questionable any extrapolation of treatment studies from the developing to the developed world.[127]

When intracranial hypertension following TBI is refractory to first-line treatments, the Brain Trauma Foundation guidelines suggest the use of decompressive craniectomy or high-dose barbiturate therapy (i.e., barbiturate coma) as second-tier strategies.[35,128] Uncertainty surrounds the decision to choose either treatment option. Each strategy has its own strengths and limitations, and they have not been compared directly in a randomized controlled trial. Previous relevant studies are summarized in Table 1.6. Cooper et al. compared decompressive craniectomy with medical treatment, which, in some cases, may or may not have included barbiturate

coma.[129] They found that craniectomy effectively lowered ICP, had no effect on mortality, and was associated with a greater risk of poor functional outcome at 6 months in an unadjusted analysis.[129] This trial raised questions about the role of this procedure in the management of severe TBI due to the poor quality of life and substantial cost of long-term care for severely disabled patients. However, critics of this trial have highlighted the unbalanced treatment groups, considerable variability in medical treatments for the control group, high cross-over rate to the surgical arm, and relatively short follow-up time as arguments against wide application of the study findings.[130,131] Eisenberg et al. compared barbiturate coma to other medical options for refractory intracranial hypertension following TBI in a randomized trial. That trial showed that barbiturates were more effective at controlling high ICP, and responders were more likely to survive.[132] However, the long-term functional outcome of the survivors was not examined in that trial. Moreover, barbiturates are associated with a high risk of systemic hypotension, which can exacerbate secondary brain injury and thereby increase the risk of mortality and poor neurological recovery.[66,132,133] Hence, considerable uncertainty surrounds which of these strategies is more effective and economically attractive in the long-term.

The optimal timing of tracheostomy in patients with severe TBI is controversial. Previous observational studies have been challenged through confounding by indication and immortal time bias, and interventional studies have rarely enrolled patients with isolated TBI.[134,135] The results of the previous studies of tracheostomy timing in TBI are summarized in Table 1.7. In addition to the small sample size in the majority of the previous studies, none of the studies was restricted to patients

with isolated TBI who have no significant multisystem injuries.[110,136-140] Multisystem trauma might increase the risk for long-term ventilator dependency and alter the unique potential advantage of early tracheostomy in TBI patients.[141,142] Moreover, the surprising finding of higher mortality with early tracheostomy in some of the previous studies suggests that residual confounding might have significantly biased their results.

Conceptual Framework for Examining the Relationship between Process of ICU Care and Outcome Following Traumatic Brain Injury

The conceptual framework of my thesis is based on the Donabedian model.[103] According to this model, information about health services can be drawn from three interconnected domains: structure, process of care, and outcomes. While the focus of the thesis is on understanding the relationship between the latter two domains, process of care and outcome, the data analyses will account for the potential modification of this relationship by important structural factors, such as the volume of TBI patients per center and trauma center designation, to capture the complexity of healthcare delivery.

ICU processes of care are not expected to be of uniform benefit to all patients in all healthcare settings.[143] In this thesis, I focus on studying a homogeneous group of TBI patients cared for in a defined healthcare setting. The population of interest is patients who sustained acute severe TBIs via a blunt mechanism, did not have

significant injury to other body regions, and were admitted to an ICU in a level I or II trauma center in the United States. Furthermore, the relationship between process and outcome will be examined in specific subgroups of this population.

The clustering of TBI patient management strategies at different hospitals is expected and could potentially lead to clustering of patients' outcomes. Therefore, the hierarchical structure of the data is accounted for during the statistical analysis of the relationship between process of ICU care and TBI outcomes in this thesis.

Although both the population of interest and the healthcare setting are focused, the thesis examines multiple processes of care delivered at different time points during the ICU stay. Therefore, examining the relationship between these processes and outcome carries different methodological challenges, and consequently different analytic methods are applied to study different processes. Throughout, the goal is to introduce multiple methods and analytical approaches that can be applied to similar processes of care in future studies of TBI patients.

General Objectives of the Thesis

1. To determine the association between ICP monitoring and mortality after severe TBI at the patient-level and at the hospital-level.

2. To determine the most effective, in terms of quality-adjusted life expectancy, and economically attractive treatment strategy for refractory intracranial hypertension following severe TBI.

3. To ascertain whether early tracheostomy, compared to late tracheostomy, in severe TBI patients is associated with shorter mechanical ventilation and shorter ICU and hospital length of stay.

CHAPTER 2: Intracranial Pressure Monitoring in Severe Traumatic Brain Injury

The purpose of this chapter is to:

1. Determine the association between intracranial pressure monitoring and mortality after a severe TBI at the patient level.
2. Determine the association between rates of intracranial pressure monitoring at the hospital level and hospital TBI-related mortality.
3. Describe the extent and determinants of inter-hospital variation observed in TBI mortality.
4. Introduce general methods that can be used to examine other potential determinants of inter-hospital variation in TBI outcomes.

Acknowledgment: parts of this chapter were reprinted from: Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *J Neurotrauma.* Oct 15 2013;30(20):1737-1746, with permission from Mary Ann Liebert, Inc., publishers. I also would like to acknowledge my co-authors: Robert A. Fowler, Todd G. Mainprize, Damon C. Scales, Alexander Kiss, Charles de Mestral, Joel G. Ray and Avery B. Nathens for granting permission to reproduce this material.

Summary

While existing guidelines promote the utilization of intracranial pressure (ICP) monitoring in patients with TBI, the evidence suggesting benefit is limited. To evaluate the impact on outcome, I determined the relationship between ICP monitoring and mortality in hospitals participating in the American College of Surgeons Trauma Quality Improvement Program (TQIP). Data on 10,628 adults with severe TBI were derived from 155 TQIP centers over 2009-2011. Random-intercept multilevel modeling was used to evaluate the association between ICP monitoring and mortality after adjusting for important confounders. I evaluated this relationship at the patient-level and at the institutional-level.

Overall mortality (n=3,769) was 35%. Only 1,874 (17.6%) patients underwent ICP monitoring, with a mortality of 32%. The adjusted odds ratio for mortality was 0.44 (95% confidence interval: 0.31-0.63) comparing patients with ICP monitoring to those without. It is plausible that patients receiving ICP monitoring were selected because of an anticipated favorable outcome. To overcome this limitation, I stratified hospitals into quartiles based on ICP monitoring utilization. Hospitals with higher rates of ICP monitoring use were associated with lower mortality: the adjusted odds ratio of death was 0.52 (95% confidence interval: 0.35-0.78) in the quartile of hospitals with highest use compared to the lowest. ICP monitoring utilization rates explained only 9.9% of variation in mortality across centers. Results were comparable irrespective of the method of case-mix adjustment.

In this observational study, ICP monitoring utilization was associated with lower mortality. However, variability in ICP monitoring rates contributed only modestly to variability in institutional mortality rates. Identifying other institutional practices that impact on mortality is an important area for future research.

Background

After the initial brain injury, mass lesions, an increase in brain water content (edema) and an increase in blood volume, can result in rising pressure in the rigid skull, which may lead to brain tissue herniation, impaired cerebral perfusion and, without intervention, further damage to the brain.[116] Among those who die from TBI, the majority die because of uncontrolled intracranial hypertension, mostly within the first 48 hours of injury.[144,145] After a severe TBI, efforts are focused on the prevention of further damage through intensive monitoring and prompt intervention. In 1951, Guillaume and Janny first described continuous ICP monitoring using an electronic magnetic transducer to measure changes in ventricular fluid pressure.[146,147] Since then, invasive ICP monitoring has become an increasingly employed tool to care for patients with severe TBI and has been recommended by the Brain Trauma Foundation guidelines for the management of severe TBI, based on indirect evidence in which observational studies linked increased ICP with worse outcomes.[114,132,148,149]

Despite its use, the effectiveness of ICP monitoring technology has not been well established.[147,148] Moreover, several recent studies examining the relationship between utilization of ICP monitors and outcome have questioned the benefit of ICP monitors in severe TBI.[121,150-154] In practice, there appears to be a low level of confidence among clinicians that ICP monitoring confers a benefit to TBI patients. According to a survey of practicing neurosurgeons in Canada, only 20% are highly confident that the routine use of ICP in severe TBI improves outcome.[155] The increasing number of studies that challenge the benefit of invasive ICP monitoring and the limited confidence in its utility might explain the reported wide variability in the utilization of ICP monitoring across centers.[118,150,156] Further, this variability might in part account for wide differences in institutional TBI-related mortality.[157-159]

In this context, I conducted an observational cohort study using data derived from the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP). The objectives of this study were as follows: 1) to determine the association between ICP monitoring and mortality after a severe TBI; 2) to determine the association between rates of ICP monitoring at the institutional level and hospital TBI-related mortality; and, 3) to describe the extent and determinants of inter-hospital variation observed in TBI mortality.

Methods

Study Design

This was an observational cohort study with the exposure of interest being invasive ICP monitoring in patients with severe TBI. The main purpose of this study was to examine the relationship between ICP monitoring and in-hospital mortality. I used two analytic approaches to assess this relationship. First, I used ICP monitoring as a patient-level variable to determine the association between ICP-monitoring and patient mortality. Second, because it is plausible that physicians elected to place ICP monitors because of an anticipated favorable or unfavorable outcome and the likelihood of similar distribution of unmeasured confounders within hospitals, I defined a hospital-level ICP monitoring utilization rate and evaluated this factor as a determinant of hospital TBI-related mortality. The study was approved by the research ethics board of Sunnybrook Health Sciences Center, Toronto, Ontario, Canada.

Data Source

I used data derived from The American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP). TQIP was created to provide an opportunity for trauma centers to compare their processes of care and risk-adjusted outcomes with their peer centers.[160] As of late 2011, TQIP includes 155 ACS-verified level I and II trauma centers across the United States and Canada. More than 100 patient and institutional variables are recorded by trained abstractors, including patient demographics, comorbid conditions, type and mechanism of injury, injury severity, prehospital and emergency department (ED) physiological variables, in-hospital

procedures and complications, and outcome information, including in-hospital mortality and discharge disposition.[160] The reliability of the data is ensured through intensive training mechanisms for the abstractors and interrater reliability audits of the participating sites.[161]

The inclusion criteria for patient entry into TQIP require at least one valid trauma International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code in the range of 800–959, excluding the late effects of trauma (905–909).[160]

Assembly of the Study Cohort

I identified all patients aged 16 years or older who were admitted between January 1, 2009 and December 31, 2011 to a TQIP hospital with an Abbreviated Injury Score (AIS) for the body region Head ≥ 3. For the purpose of this study, I selected those patients who met the Brain Trauma Foundation level II recommendation for ICP monitoring: those with an acute intracranial lesion and severe TBI [defined as a total Glasgow Coma Scale Score (GCS) in the emergency department ≤8]. The exclusion criteria were as follows: other severe injuries (AIS > 2) in any other body region, penetrating TBI, "non-survivable" TBI (head AIS=6), dead on arrival, and prior advanced directives to withhold life-sustaining interventions.

Identification of Exposure

Patients undergoing ICP monitoring were identified by the presence of any one of the following ICD-9-CM procedure codes: 01.10 (insertion of catheter or probe for intracranial pressure monitoring), 01.16 (insertion of catheter or probe for

monitoring partial pressure of brain oxygen), 01.17 (insertion of catheter or probe for monitoring brain temperature), or 02.2 (ventriculostomy).

Patient-level Covariates

The following patient-level covariates were considered for inclusion into adjusted analyses: age, gender, race, comorbid illnesses, injury mechanism and severity, vital signs in the emergency department including GCS motor and total scores, type of intracranial lesion, and insurance status. To identify acute intracranial lesions, I used the AIS predot codes (1998 version) that reflect injuries to the intracranial structures (Table 1.4).

Hospital-level Covariates

To characterize hospital environment that might influence TBI process of care and outcome, I classified centers based on the following factors: volume of TBI patients per center during the study period (divided into quartiles), teaching status, number of hospital beds, hospital type (nonprofit versus for-profit) and ACS or state trauma center designation level.

Outcome Measure

The primary endpoint for this study was the odds of in-hospital death after TBI.

Statistical Analysis

I calculated standardized differences to compare baseline characteristics between those who underwent ICP monitoring and those who did not.[162,163] Standardized

differences represent the mean difference as a percentage of the standard deviation. To estimate these, differences between groups are divided by the pooled standard deviation of the two groups. The advantage of standardized differences is that they are not as sensitive to sample size as traditional tests and provides a sense of the relative magnitude of differences.[162,163] Standardized differences greater than 0.1 are typically considered meaningful.[162] Two random-intercept multilevel logistic regression models were used to examine the adjusted association of patient-level and hospital-level variables with in-hospital mortality after accounting for the clustering of patients within centers. The main exposure for the first model was ICP monitoring as a patient-level factor. For the second model, the hospital-specific ICP utilization rate (categorized into quartiles), as a hospital-level factor, was the main exposure. Random-intercept regression models are standard multivariable regression models that include an extra term to account for the random differences in TBI mortality between the various hospitals. Covariate selection for both models was performed using the change in estimate approach described by Mickey and Greenland.[164] The final models included patient- and hospital-level covariates (described in the results section) in addition to clinically meaningful interaction terms that changed the estimate of the main exposure by >10% in either direction. I checked for multicollinearity within each model using the tolerance statistic and variance inflation factor.

For both of the models, discrimination was estimated using the c-statistic, and calibration was assessed using observed-versus-predicted outcome plots. In addition, I used the squared Pearson correlation between the observed and

expected outcomes to measure the proportion of explained variation by each model.[165]

To quantify the variability among hospitals in TBI mortality, I used the median odds ratio instead of the intraclass correlation coefficient because of the interpretational difficulty of intraclass correlation coefficient with multilevel logistic regression models.[166,167] The median odds ratio corresponds to the median value obtained when comparing the adjusted odds of dying after TBI if the same patient was admitted to two different randomly selected hospitals.[166,167] It estimates unexplained heterogeneity across different hospitals after adjusting for patient-level covariates.[168] In contrast to the intraclass correlation coefficient, the median odds ratio is statistically independent of the prevalence of the outcome of interest.[166] In addition, it is easy to interpret because its magnitude can be directly compared with the odds ratios of the patient-level variables.[168] The proportion of inter-hospital variance in mortality that can be explained by hospital-specific ICP monitoring rate was calculated using the proportional change in variance.[169] proportional change in variance can be calculated as per the following equation:

$$PCV=[(V_1-V_2)/V_1]\times 100$$

where V_1 is the inter-hospital variance in a multilevel model that lacks ICP monitoring rate as a hospital-level factor, and V_2 is the inter-hospital variance in the same model after adding hospital-specific ICP monitoring rate.[166,169]

Sensitivity Analyses

Adjusted Analysis Using Propensity-score Methods

First, I constructed a logistic regression model with ICP monitoring as the outcome variable and the baseline patient and hospital characteristics as the explanatory variables to calculate the probability of an individual patient to receive an ICP monitor. Patient-level covariates in the propensity score model were: age, gender, race, comorbid illnesses, injury mechanism and severity, vital signs in emergency department including GCS motor and total scores, type of intracranial lesion, and insurance status. Hospital-level covariates were: volume of TBI patients and teaching status. Inverse probability weighting was then used to adjust for differences between patients who received ICP monitors and those who did not. This approach involves weighting individual patients who underwent ICP monitoring by the inverse probability that he/she would undergo ICP monitoring and weighting patients who did not receive ICP monitoring with the inverse probability that he/she would not undergo ICP monitoring. I assessed the performance of the propensity model by comparing the distribution of covariates between ICP and no ICP groups before and after adjustment using inverse probability weighting. Finally, I combined inverse probability weighting and model-based approach for a 'doubly robust' analysis, as described by Lunceford and Davidian, to examine the association between ICP monitoring and mortality.[170] Compared to other propensity-score methods, inverse probability weighting using the doubly robust estimator appears to have superior performance in estimating differences in proportions in simulation studies.[171]

The Individual-level Relationship between ICP Monitoring and Mortality within Different Hospital Quartiles of ICP Use

Because there may be quartile-level confounding from unmeasured or unappreciated variables that might potentially lead to ecological fallacy[172], I also examined the individual-level relationship between ICP monitoring and mortality in hospitals within each quartile. Each subgroup analysis was adjusted for patient and hospital-level variables in a similar fashion to the primary analysis.

All of the statistical analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina), and statistical significance was defined by a two-tailed P value <0.05.

Results

The study cohort consisted of 10,628 patients with severe TBI with an acute intracranial lesion who were admitted to 155 level I and II trauma centers across the United States and Canada between January 2009 and December 2011. Overall mortality (n=3,769) was 35.5%. Only 1,874 (17.6%) patients underwent ICP monitoring, with a mortality of 31.6%. The median time from emergency department presentation to ICP monitor insertion was 3.1 hours (interquartile range: 1.85-7.25 hours]. In contrast to the patients managed without ICP monitoring, the ICP-monitored group were younger, presented with fewer comorbid illnesses, suffered more severe TBIs (as measured by head AIS), and were more

likely to have traumatic subarachnoid hemorrhage, compressed/absent basal cisterns, brainstem, cerebellar or intracerebral mass lesion, epidural hematoma, or subdural hematoma (Table 2.1). Conversely, patients managed without ICP monitors were more likely to have experienced fall-related injuries, presented with hypotension (systolic blood pressure <90 mmHg), were without commercial insurance, and were cared for at non-teaching hospitals. There was no significant difference between the two groups in either the total or motor GCS scores in the emergency department (Table 2.1).

When the 155 hospitals were ranked into quartiles based on their rate of ICP monitoring, there was considerable inter-hospital variation in ICP monitoring with a median utilization rate of 16% (IQR: 8–26%). This large variation was accompanied by differences in the patient and hospital characteristics across the four quartiles (Table 2.2). In quartile 4 (highest ICP monitoring rate), patients had more severe injuries (as measured by head AIS) and presented with more comorbid illnesses. In contrast, non-teaching hospitals were more likely to be in quartile 1 and 2. Overall mortality was 35.6% (n=910) in quartile 1, 38.2% (n=939) in quartile 2, 35.3% (n=1136) in quartile 3 and 32.7% (n=784) in quartile 4.

Relationship between ICP Monitoring and Mortality at the Patient Level

I evaluated the association between ICP monitoring and in-hospital mortality at the patient level using a random-intercept multilevel model. Using this approach, ICP monitoring was associated with significantly lower odds of death (odds ratio 0.44, 95% confidence interval 0.31–0.63, p<0.0001). In addition, admission to a center

with a higher volume of TBI patients as opposed to a lower volume center was associated with lower mortality (p=0.01). By contrast, all of the following were associated with a higher risk of death: increasing age, fall-related injuries, a lower GCS motor score in the emergency department, a higher head AIS, the presence of traumatic subarachnoid hemorrhage, intracerebral mass lesion, compressed/absent basal cisterns, brainstem/cerebellar lesion, hypotension on admission, and a number of comorbid illnesses, including coronary artery disease, renal failure requiring dialysis, cancer and bleeding disorders (Table 2.3). When introducing interaction term with age, the association between ICP monitoring and lower mortality was more pronounced in patients aged ≤65 years (odds ratio 0.35, 95% confidence interval 0.23-0.54) as opposed to older patients (odds ratio 0.60, 95% confidence interval 0.44-0.83). No significant interaction was found between ICP monitoring and motor GCS score on admission (p=0.44).

This regression model showed good discrimination (C statistic 0.86) and calibration (based on an observed-versus-predicted plot), and explained 61.1% of the observed variation in mortality across patients.

Relationship between ICP Monitoring and Mortality at the Hospital Level

After adjustment for the patient- and hospital-level factors in a random-intercept multilevel model, there were significant differences in the mortality rate across quartiles (Figure 2.1). Compared to the quartile with the lowest ICP monitoring rate (quartile 1), the adjusted odds ratio of dying in the hospital after TBI was 0.52 (95% confidence interval: 0.35-0.78) for quartile 4, 0.63 (95% confidence interval: 0.43-

0.93) for quartile 3 and 0.72 (95% confidence interval: 0.48-1.06) for quartile 2. This regression model had good discrimination (C statistic 0.86) and good calibration (based on an observed-versus-predicted plot), and explained 61.2% of the observed variation in TBI in-hospital mortality.

The median odds ratio for TBI in-hospital mortality across the various hospitals was 1.48. In other words, the median adjusted odds of dying after TBI were 1.48-fold greater if the same patient was admitted to one randomly selected hospital as opposed to another. In a similar model that had the same patient- and hospital-level factors but lacked the hospital-specific ICP monitoring rate, the proportional change in inter-hospital variance in TBI mortality after adding the hospital-specific ICP monitoring rate (categorized into quartiles) was -9.89%, indicating that 9.89% of the inter-hospital variation in TBI mortality could be attributed to the hospital-specific ICP monitoring utilization rate.[169] Similarly, the volume of TBI patients per center could explain an additional 3.63% of this variation. However, this inter-hospital variation was not explained by the hospital teaching status (p=0.97) or number of hospital beds (p=0.53).

Sensitivity Analyses

Adjusted Analysis Using Propensity-score Methods

The distributions of individual and hospital characteristics were well balanced between ICP and no ICP groups after adjustment using inverse probability weighting (Table 2.4). Using a 'doubly robust' inverse-probability-weighting

estimator with a multilevel logistic regression model to predict mortality, the adjusted association between ICP monitoring and lower mortality was also significant (odds ratio 0.50, 95% confidence interval: 0.43–0.59, p=<0.0001).

The Individual-level Relationship between ICP Monitoring and Mortality within Different Hospital Quartiles of ICP Use

Within each quartiles of hospital ICP monitoring use, the findings were consistent with both the overall patient-level associations and quartile-adjusted associations (Table 2.5). ICP monitoring was associated with lower adjusted odds of patient mortality regardless of which hospital quartile patients received care.

Discussion

In the field of neurotrauma and critical care, invasive ICP monitoring has long been considered the standard of care for severe TBI patients without being supported by rigorous assessment of its effectiveness in improving outcomes.[173] In this study, I demonstrated a strong association between ICP monitoring and a lower risk of death after severe TBI. This finding was consistent when I examined the effectiveness of this technology at either the patient or hospital level. Further, there appeared to be a dose-response, with higher rates of ICP monitoring associated with lower rates of mortality, lending further credence to a causal relationship.

Accurate and continuous ICP monitoring via an invasive tool can lead to the prompt recognition of spiking pressure around the injured parts of the brain.[116] Such recognition could potentially lead to timely intervention that is able to control the rising pressure inside the rigid skull, a process that is thought to be the leading cause of death among severe TBI victims, especially during the first 48 hours after injury.[144,145] Despite the plausibility of its efficacy in guiding us to provide better care, many have questioned its effectiveness based on several studies that failed to provide conclusive and consistent results. This inconsistency among previous studies might explain the wide variability in ICP monitoring utilization across different hospitals.[22] The study findings agree with a number of previous studies that support the value of ICP monitoring in TBI,[118,119] but contrast with several studies that either failed to show an association between ICP monitoring and better outcomes,[124,150,151,153,154,174] or showed an association between ICP monitoring and higher mortality.[121] However, previous observational studies in this area have generally suffered from several limitations, including small sample size, a lack of or inadequate adjustment for multiple important confounders and selection bias.[122,123,175] In addition, the clustering of ICP management strategies for TBI at different hospitals is expected and would potentially lead to a clustering of the patient outcomes. Accounting for such clustering during statistical analysis in TBI studies, including ICP monitoring studies is commonly overlooked.[121,151,154,156,157] The only randomized trial in this area showed no difference in the primary outcome, a composite measure based on performance across 21 measures of functional and cognitive status, between care focused on maintaining ICP at 20 mm Hg or less and

care based on imaging and clinical examination in the setting of countries in the developing world where ICP monitoring is very rarely used.[124] However, the trial was not sufficiently powered to detect small but important mortality differences between both groups.[124] In addition, differences in injury characteristics, prehospital, ICU and post-ICU structure and processes of care, and the observation of 'delayed mortality' due to medical complications, accounting for more than one third of deaths following TBI in Latin America, may render questionable any extrapolation of the results from this randomized trial to other countries where delayed mortality is much lower.[127]

In my study, I found considerable unexplained variation in hospital mortality even after accounting for measured patient- and hospital-level characteristics. Moreover, the data were derived from verified trauma centers that have interest in high-quality care by virtue of their participation in TQIP and quality improvement activities. For that reason, study hospitals may have lower mortality rates than hospitals not participating and this may have underestimated the extent to which in-hospital mortality varies across hospitals. Upon examining the determinants of this variation, I found that the utilization rate of ICP monitoring explained less than 10% of the inter-hospital variation in severe TBI mortality. Albeit to a smaller extent, volume of TBI patient per center was another determinant of this variation. Other factors that might further explain inter-hospital variation in TBI mortality and were not examined in this study include variations in community or institutional approach toward withdrawal of life-sustaining therapy.[176] Identifying other institutional practices that impact on mortality is an important area for future

research.

This is the largest study of ICP monitoring in TBI to date. The strengths of the study include the broad selection criteria, adjustment for multiple important confounders and accounting for the hierarchical structure of the data during the statistical analysis. However, the study results should be interpreted with caution. The findings of this study are limited mainly by lack of information about certain potential confounders. For example, the database I used lacked information on pupillary abnormalities that are known to be strong predictors of poor outcome after TBI. However, recent evidence suggests that ICP-monitored patients are more likely to have pupillary abnormalities than those patients managed without invasive ICP monitoring.[150] Therefore, I do not expect that accounting for pupillary reactivity will change the direction of observed association. In addition to the patient characteristics, the decision to insert an ICP monitor in a TBI patient involves multiple considerations, including physician judgment, the course of the patient during the hospital stay, and the availability of trained staff. These nuances are not measured in the source data. However, I attempted to adjust for measured confounders in addition to adding an extra term to account for the random differences in TBI mortality between different hospitals using a random-intercept multilevel model with ICP monitoring as a patient-level variable, I repeated the analysis with ICP monitoring rate as a hospital-level factor, and I used propensity score (representing the probability that patients would be selected for ICP monitoring) methods to reduce selection bias. Each of these analytic approaches provided results that support the benefit of utilizing ICP monitoring technology in

severe TBI.

In studies of TBI mortality, the ideal outcome measure would include deaths after acute care hospitalization. However, prior studies have shown that TBI-related death after hospital discharge is uncommon.[177-179] In a population-based cohort study of hospitalized TBI patients who were discharged alive, about 92% of those patients were alive at 15 months after discharge.[180] Among post-discharge deaths, only 17% were TBI-related.[180] Limited by the database, I could not assess the relationship between ICP monitoring and other important outcome measures, including long-term functional and quality of life outcomes. Future studies are required to examine these important relationships.

Until further observational studies with rigorous adjustment for potential confounding factors or more randomized clinical trials become available, I recommend wider utilization of ICP monitoring technology in the management of patients with severe TBI and abnormal computerized tomography findings to better inform medical decisions and guide more prompt interventions. However, variability in ICP monitoring rates contributed only modestly to inter-hospital variability in TBI mortality. Identifying other institutional practices that impact on mortality is an important area for future research.

CHAPTER 3: Management of Refractory Intracranial Hypertension Following Traumatic Brain Injury

The purpose of this chapter is to:

1. Examine the comparative effectiveness of commonly used treatments for refractory intracranial hypertension following TBI, decompressive craniectomy and barbiturate coma, in terms of quality-adjusted life expectancy.

2. Compare the cost consequences of decompressive craniectomy and barbiturate coma among patients with refractory intracranial hypertension following TBI from the perspective of a healthcare payer in the United States.

3. Evaluate the impact of patients' age on the relative economic attractiveness of decompressive craniectomy and barbiturate coma in treating refractory intracranial hypertension following TBI.

4. Identify the major drivers of decision uncertainty and examine the value of future research.

5. Introduce economic evaluation methods that can be applied to weigh the relative costs and benefits of alternative courses of action in the management of severe TBI patients.

Acknowledgment: Parts of this chapter were reprinted from: Alali AS, Naimark DM, Wilson JR, et al. Economic evaluation of decompressive craniectomy veruss barbiturate coma for refractory intracranial hypertesnion following traumatic brain

injury. *Critical care medicine.* (In Press), with permsision from Lippincott Williams & Wilkins. I would like to acknowledge my co-authors: David M. J. Naimark, Jefferson R. Wilson, Robert A. Fowler, Damon C. Scales, Eyal Golan, Todd G. Mainprize, Joel G. Ray and Avery B. Nathens for granting permission to reproduce this material. I also wish to thank Cynthia Harrison-Felix, PhD (Project Director, Traumatic Brain Injury Model Systems National Data and Statistical Center, Craig Hospital, Englewood, CO) for her assistance with obtaining data from the Traumatic Brain Injury Model Systems National Database, and Murray D. Krahn, MD, MSc (Toronto Health Economics and Technology Assessment Collaborative, University of Toronto, Toronto, ON) for his insightful feedback on the utility scores for temporary health states in the decision-analytic model presented in this chapter.

Summary

Decompressive craniectomy and barbiturate coma are often used as second-tier strategies to manage refractory intracranial hypertension following severe TBI. The relative effectiveness and economic attractiveness of these two treatment options is unclear, however.

I performed a cost-utility analysis of decompressive craniectomy versus barbiturate coma using a Markov Monte Carlo microsimulation model, with a life-long time horizon. I compared quality-adjusted survival and cost of each treatment, using a healthcare payer perspective. Model parameters were estimated from published studies. Two-dimensional simulation was used to incorporate parameter uncertainty into the model. Value of information analysis was conducted to identify

major drivers of decision uncertainty and focus future research. The base case was a population of patients (mean age=25 years) who developed refractory intracranial hypertension following TBI.

Decompressive craniectomy was associated with an average gain of 1.5 quality-adjusted life years (QALYs) relative to barbiturate coma, with an incremental cost-effectiveness ratio (ICER) of $9,565/QALY gained. Decompressive craniectomy resulted in a greater quality-adjusted life expectancy 86% of the time, and was more cost-effective than barbiturate coma in 78% of cases if our willingness-to-pay threshold is $50,000/QALY, and 82% of cases at a threshold of $100,000/QALY. At older age, decompressive craniectomy continued to increase survival but at higher cost (ICER=$197,906/QALY at mean age=85 years).

Among patients with refractory intracranial hypertension following severe TBI, decompressive craniectomy provides better value in terms of costs and health gains than barbiturate coma. The relative economic attractiveness of decompressive craniectomy might be less apparent among older patients. Further research, particularly on natural history of severe TBI patients, is needed to make more informed treatment decisions.

Background

Severe TBI accounts for only 10% of all head injuries [82], but it contributes to the greatest proportion of death, disability and TBI-related costs.[87,88] The most common

acute cause of death and disability within this patient group is the development of uncontrolled raised ICP.[144,145] Several first-tier medical strategies are available to treat high ICP including: hyperosmolar therapy, normalization of arterial carbon dioxide level, optimal sedation, neuromuscular blockade and external ventricular drainage.[35,39,40] However, about 10-15% of patients develop intracranial hypertension refractory to these first-tier strategies.[107,181] To control such refractory ICP elevations, the two second-tier therapies most commonly considered are decompressive craniectomy and barbiturate coma, in accordance with the Brain Trauma Foundation guidelines.[35,107,124,128,181,182]

Each strategy presents its own strengths and limitations, and there are no published randomized controlled trials comparing these two treatments directly. Decompressive craniectomy involves the removal of a large portion of the skull and effectively lowers ICP and prolongs survival.[129] However, a substantial proportion of survivors are severely disabled, which raises questions about the role of this procedure in the management of severe TBI due to the poor quality of life and substantial cost of long-term care for severely disabled patients.[129,183,184] Furthermore, patients who undergo decompressive craniectomy are at higher risk for post-traumatic hydrocephalus, and usually require further surgeries to reconstruct the skull if they survive.[129] Barbiturate coma involves the administration of high doses of intravenous barbiturate drugs, which suppress cerebral metabolism and thereby reduce ICP.[185] This strategy is not known to increase disability amongst survivors, and it is not associated with upfront surgical morbidity.[186] However, not all patients treated with barbiturates experience ICP

reduction.[132] Moreover, barbiturates are associated with a high risk of systemic hypotension, which can cause secondary brain injury and increase the risk of mortality and worsen long-term outcomes.[66,132,133] Hence, considerable uncertainty surrounds which of these strategies is more effective and economically attractive.

The goal of the current study was to investigate which of these therapies, decompressive craniectomy versus barbiturate coma, provides better value in terms of costs and health effects for patients with refractory intracranial hypertension following severe TBI.

Methods

I conducted a cost-utility analysis to compare decompressive craniectomy and barbiturate coma for the treatment of intracranial hypertension following severe TBI.

Study Design: Microsimulation

To investigate the study question, I constructed a discrete-time, discrete-space, Markov model which employed microsimulation. Such microsimulation models simulate an individual hypothetical patient's clinical course by defining a set of distinct, mutually exclusive, health states and following the transitions that the individual makes between the health states over time. The use of microsimulation, as opposed to cohort analysis, allows for individual patient variability with respect

to attributes, such as demographics and injury severity, which affect long-term outcome.[68] Microsimulation also facilitates incorporation of model "memory" through tracker variables, which allow for clinical events experienced by the hypothetical patient to affect the subsequent probabilities of transition among the health states. I defined a microsimulation trial as the life experience of a single hypothetical individual from entry into the model until death. Each trial consisted of two parts: first I ran the hypothetical individual through the model structure representing one strategy and then through structure representing the other. Details of these structures are provided below. I assigned an incremental cost and quality-of-life weight (utility) to each health state. Thus, during the course of a trial, as a hypothetical patient traversed health states, he or she accrued both costs and quality-adjusted life months. Upon death, the cumulative total of these quantities represented the individual's total life-time costs and quality-adjusted life-span, respectively. For each simulated individual, I derived two sets of these cumulative totals: one for each of the two strategies. By averaging these values across a large number of trials, I achieved stable estimates of the relative expected costs and quality-adjusted life expectancy associated with the two strategies.

O*utcomes, Time Horizon and Perspective*

Outcomes of interest were costs and quality-adjusted life expectancy. The modeled time horizon was life-time, that is I followed up each simulated patient from entry into the model until death. Time elapsed during trials was broken up into discrete segments or cycles with the cycle length set at 1 month. Costs in 2013 US dollars

were considered from the perspective of a healthcare payer in the United States. All analyses were performed in accordance with good modeling practices [187-190] using TreeAge Pro 2013 software (TreeAge Software Inc, Williamstown, MA). The study was approved by the research ethics board of Sunnybrook Health Sciences Center, Toronto, Ontario, Canada.

Model Structure

Selection of Hypothetical Patients

Hypothetical patients were men or women with a severe TBI [Glasgow Coma Scale (GCS) = 3-8] and intracranial hypertension (>20 mm Hg) that was not responsive to first-line ICP lowering therapies administered in accordance with the Brain Trauma Foundation guidelines, including: hyperosmolar therapy, normalization of arterial carbon dioxide level, optimal sedation, neuromuscular blockade, and external ventricular drainage.[35,39,40] Patients with bilaterally fixed and dilated pupils were not considered in this analysis since their treatment is typically deemed futile and brain death is often considered inevitable. At the start of each trial, individual patient characteristics, including age, GCS motor score, and pupillary reactivity were sampled from specified distributions (Table 3.1). Distributions were specified rather than using fixed attributes in order to reflect variability in the characteristics of severe TBI patients who present with refractory intracranial hypertension as described in previous studies of this patient population.[129,186] Consequently, these attributes varied among trials (i.e. among hypothetical patients). Subsequent to

selection of a hypothetical subject's initial attributes, he or she entered each of the strategies in turn.

Decompressive Craniectomy Strategy

Multiple variations of the craniectomy procedure have been described.[129] A surgeons' decision to employ one variation typically depends on the specific characteristics of the patient under consideration and local practice patterns. For my model, I assumed that craniectomy involves a large bifrontotemporoparietal craniectomy with bilateral dural opening to maximize ICP reduction. Further technical variations of the procedure (e.g., division of the sagittal sinus) were assumed to have similar efficacy and complication profile (Figure 3.1). Hypothetical patients who underwent craniectomy entered the subsequent Markov model (Figure 3.2).

Barbiturate Coma Strategy

Barbiturate coma was defined as high-dose intravenous barbiturate therapy, as described in the Brain Trauma Foundation guidelines (e.g. pentobarbital infusion at a rate of 1 mg/kg/hour, or thiopental infusion at 3 mg/kg/hour).[35] As suggested by previous studies, differences in the efficacy and complications among individual barbiturate agents were assumed to be negligible for the purposes of this study.[186] The initial chance node in the barbiturate coma strategy (Figure 3.1) captured the possibility that intracranial hypertension could not be controlled using barbiturate therapy. Hypothetical patients who failed to respond to barbiturates were modelled

to undergo decompressive craniectomy, which reflects common clinical practice (Figure 3.1).

Hypotension Modeling

During each trial, the simulated subject experienced, or did not experience, systemic hypotension at or soon after the time of intervention according to a strategy-specific probability distribution obtained from the literature.[132,191] For both strategies, the occurrence of hypotension was captured by a tracker variable and it affected patient's long-term outcome by subsequently influencing his/her transition probability to one of the long-term health states.

Subsequent Short-term Health States

A common Markov health state structure was employed for both strategies which included a short-term period, representing the first 6 months after intervention, and a long-term period, representing the period after the first 6 months until patient death (Figure 3.2). Although a common health state structure was employed for the two strategies, the transition probabilities between health states differed between them as described below.

All simulated patients began in the "month 1" health state, which represented the first month following an intervention for refractory intracranial hypertension that patients usually spend in an acute care hospital, as per previous studies of this patient population.[129,181] Hypothetical patients faced the possibility of post-traumatic hydrocephalus or death during each 1-month cycle in the short-term

period. Hypothetical patients were modeled to undergo ventriculoperitoneal (VP) shunt insertion if hydrocephalus developed. Such patients may develop shunt complications, such as shunt blockage or infection, at any point thereafter, which may require hospitalization for treatment and shunt revision. The risk of these complications were modeled to depend on the elapsed time since the shunt surgery, with the highest risk occurring during the first year after shunt insertion. I assumed that all decompressive craniectomy patients who survived for six months underwent cranioplasty.

Although TBI patients are prone to experience other clinical events, I focused on modelling complications whose probabilities are expected to vary based on the treatment strategy.

Subsequent Long-term Health States

All survivors at the end of the first 6 months were modeled to transition from the short-term period to one of the long-term functional health states (i.e., Glasgow Outcome Scale (GOS) categories). The transition probabilities within the short-term period and between short-term health states and one of the 5 GOS categories at 6 months differed based on the treatment strategy (Table 3.2). These transition probabilities differed within each strategy depending on the individual patient characteristics sampled for each trial (e.g., age, GCS motor score and pupillary reactivity) and on the occurrence of hypotension at/after applying the intervention. These probability functions were modelled using the validated International

Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model for TBI outcome.[68,192]

The regression equation was solved for the intercept for each of the GOS categories using regression coefficients from the IMPACT model and transition probability estimates from the literature. [68] Sampled characteristics (i.e., age, GCS motor score, pupillary reactivity and hypotension) were input to the relevant equation for a given trial to calculate the trial-specific transition probability to one of the GOS categories for each treatment strategy (Figure 3.3). This modelling technique is demonstrated in the following example.

While building my decision-analytic model, I calculated the intercept for the equation that estimate the individual patients' transition probability to "moderate recovery" (GOS=4) following decompressive craniectomy as follows: 1) I estimated the average probability of transitioning to "moderate recovery" at 6 months following decompressive craniectomy from the literature (P=0.26); 2) Using baseline characteristics of patients enrolled in previous randomized trials [129,186], I estimated the average patient' age (Age=25 years), GCS motor score (median GCS motor score=3), proportion of patients who have pupillary abnormalities (pupils=18%), and the proportion of patients who develop hypotension following craniectomy (hypotension=31%); 3) I input the estimates from steps 1-2 into the following equation (Figure 3.3) to derive the decompressive craniectomy strategy-specific intercept for transitioning to "moderate recovery" as follows:

ln (P/(1-P)) =Intercept+ B1*Age+B2*pupils+B3*GCS Motor Score+B4*Hypotension

ln (0.26/(1-0.26))=Intercept+(0.038*25)+(0.6*0.18)+1.1+(0.059*0.31)

Intercept= ln (0.26/(1-0.26))-0.95-0.11-1.1-0.02

Intercept=-3.23

Accordingly, if a simulated patient's age was 35 years, his/her GCS motor score on admission was 2 with normal pupils, and no history of hypotension following decompressive craniectomy, the patient-specific probability to transition to "moderate recovery" (GOS=4) at 6 months post-injury can be calculated as follows:

In (P/(1-P)) =Intercept+ B1*Age B2*pupils+B3*GCS Motor Score+B4*Hypotension

In (P/(1-P)) =-3.23+(0.038*35)+(0)+(1.74)+(0.059*0)

In (P/(1-P)) =-0.16

P/(1-P)=0.85

0.85/P-0.85=1

0.85/P=1.85

P=0.46

Transition of Patients between GOS Categories over Time

Patients' functional outcomes were not assumed to be fixed after the first year following injury. Instead, each patient could progress (or regress) between the first year and 5-7 years post-injury from their originally assigned GOS category (at 6

months post-injury). The probabilities of progression (or regression) from one GOS category to another (including death) were estimated based on Whitnall et al. findings.[193] The latter investigators prospectively followed a cohort of TBI patients (n=219) from 5 hospitals in the United Kingdom until 5-7 years after injury.[193] The comparison of GOS outcomes between 1 and 5-7 years post-injury is shown in Table 3.3. In the model, each simulated patient would change his/her GOS category according to the Whitnall et al. findings anytime between year 1 and a randomly chosen time point between 5 and 7 years following injury. After 5-7 years, functional outcomes are assumed to remain in that state (i.e. same GOS category) for life.

Model Inputs

A coauthor (Jefferson R. Wilson) and I independently searched MEDLINE using the key word "traumatic brain injury" and the subheadings "treatment" or "decompressive craniectomy" or "barbiturate" or "hydrocephalus" to derive parameter estimates to populate the model. We also searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews and Tufts Cost-Effectiveness Analysis Registry using the key word "traumatic brain injury". This search was supplemented by a review of the reference lists of key articles. The search was limited to literature in English published between January 1980 and August 2013. Disagreements were resolved through discussion and consensus.

Probabilities

All probabilities (Table 3.2) were converted from their respective study time scale into monthly probabilities for use in the model by assuming a constant hazard rate. Estimates from randomized trials, when available, were prioritized over estimates from observational studies. Transition probabilities from short-term to long-term health states (i.e., GOS categories) for both treatment strategies were obtained from randomized controlled trials. Functional outcome progression (or regression) and GOS-specific survival data during the first 5-7 years post-injury were obtained from a multicenter prospective cohort study.[193] Following the first 5-7 years post-injury, age- and sex-matched US population death rates were used to predict survival for patients in GOS category of moderate disability or good recovery.[194] Because vegetative and severely disabled patients were shown to have shorter longevity than the general population, I estimated their survival after 5-7 years post-injury by adjusting their age- and sex-matched death rates using hazard ratio estimates obtained from the literature.[180,195,196]

Quality of Life

I represented the quality of life of each health state with a utility score. Utility is a measure of the strength of one's preference for a certain health state, which ranges from 0 (death) to 1 (perfect health).[197] The quantity of quality-adjusted life months (QALMs) associated with an outcome is calculated by multiplying the utility value of the relevant health state by the duration of time spent in that health state.

The utility scores for temporary health states (within the first 6 months post-injury) were estimated by mapping those health states to the 5 domains of EQ-5D

instrument by a panel of 6 neurosurgeons, and 6 intensivists involved in the care of severe TBI patients. EQ-5D is a generic, multi-attribute, preference-based health status measure developed by EuroQol group.[198] The instrument consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[198] Each dimension has 3 levels: no health problems (level 1), some health problems (level 2), and extreme health problems (level 3).[198] Hence, the combinations 11111 and 33333 represent the best health state and the worst health state, respectively.[199] The instrument describes a total of 243 health states. [199] Empirically derived population-specific weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his/her current health state. [199] The quality-of-life scores, derived from EQ-5D questionnaire, were converted to utility scores using US population-based EQ-5D preference weights. [199]

Utility weights for GOS categories were obtained from Smits et al., in which GOS-specific quality of life scores using the EQ-5D questionnaire were measured in a subset of head injury patients.[200,201] I assumed that the utility score for vegetative state (GOS=2) was the same as death (i.e., zero) because it was not measured in the former study.

Costs

Lifetime costs were considered from the perspective of a healthcare payer and represented the sum of acute, sub-acute and long-term medical expenses accumulated over the lifetime of each simulated patient. Acute care costs included

costs associated with the ICU and subsequent hospital stay for patients with severe TBI and potential surgical procedures' fees associated with each treatment strategy.

I derived estimates for ICU and hospitalization costs per day for severe TBI patients from Whitmore et al. and Faul et al., respectively.[202,203] Then, I calculated the total cost for acute hospitalization per patient based on the sampled ICU and total hospital length of stay for each individual patient (i.e., trial). The distributions of ICU and total hospital length of stay were derived from previous studies of patients with refractory intracranial hypertension following TBI (Table 3.1).[129] For example, if a simulated patient's ICU length of stay is 10 days and the total hospital length of stay is 30 days, the acute hospitalization cost is calculated as follows:

Total hospitalization cost= (ICU days*10,450.86)+((total hospital days-ICU days)*3,483.62)

Total hospitalization cost=(10*10,450.86)+((30-10)* 3,483.62)

Total hospitalization cost=(104,508.60)+(69,672.40)=$174,181

The cost of different surgical procedures were derived from the 2013 Physician Fee Schedule Payment Amount File National/Carrier for all carriers and localities listed in the database.[204] Average costs of hospitalization related to VP shunt insertion/revision were obtained from a previous analysis of the Nationwide Inpatient Sample database.[205] Rehabilitation costs for different GOS categories were estimated from Faul et al. [203]

Estimated daily cost of nursing home care was based on 2012 Medicaid average reimbursement rates for allowable costs incurred on behalf of Medicaid patients.[206] The proportion of patients in each GOS category who reside in nursing homes at 1, 2, 5, 10 and 15 years post-injury were estimated from the National Institute on Disability and Rehabilitation Research-funded TBI Model Systems National Database (Table 3.4).[207]

All costs were inflated to 2013 US dollars using the consumer price index, medical component.[208]

Cost-utility Analysis

I applied a 3% discount rate to all future costs and health gains.[209] To overcome the limitations of standard half-cycle correction, I instead used the cycle tree approach; in which hypothetical subjects who transition between states are given half the value or cost for the state they are leaving and half of the credit for the state to which they are going.[210] The results are reported as an incremental cost-effectiveness ratio (ICER; expressed as the change in cost in US dollars per change in QALY), which represents the incremental cost for each additional QALY gained. The ICER was calculated by dividing the mean difference in costs between the two treatment strategies by the mean difference in effectiveness across trials. A specific strategy at the health policy decision level is economically attractive if the relevant ICER is less than the amount a health policy maker is willing to pay for an additional QALY. The availability of a generalizable willingness-to-pay threshold is debatable, but a commonly cited threshold is $50,000/QALY.[211] I compared the findings with

this threshold as well as a wider range of willingness-to-pay values.

Sensitivity Analyses

In order to assess overall variability in the ICER, I employed probabilistic sensitivity analysis (PSA). In the latter, internal model parameters were represented by distributions of possible values, rather than point estimates. I assumed beta distributions for probabilities and utilities, negative gamma distributions for disutilities, gamma distributions for costs, and log-normal distributions for hazard ratios [212]. Parameter distributions were randomly sampled 10,000 times. For each sample (i.e., each set of parameters), 1,000 microsimulation trials were run. Individual patient characteristics were sampled from their corresponding distributions for each trial, as described previously. In addition to calculating mean ICER and corresponding distribution across all samples, I estimated the probability that each strategy was optimal at a wide range of willingness-to-pay thresholds.

In addition, I conducted sensitivity analyses wherein the results of changing a number of key assumptions in the model were explored. First, I tested the impact of varying the mean age for simulated patients. Second, I examined the results of the model after assuming that hypotension was avoided in all patients, including patients who received barbiturate therapy. Third, I repeated analysis under the assumption that the life expectancy of all survivors after 5-7 years post-injury is reduced regardless of their GOS category. Fourth, I examined the impact of using state-specific nursing home costs instead of nationwide average on model findings. Finally, I discounted all future costs and benefits by 5% instead of the 3% discount

rate to account for a range in perspectives on relative value of near and long-term effects and expenses.

Value of Information Analyses

Because there is uncertainty surrounding the model parameters, there is a chance that the recommended course of action from the model could be wrong. That is, although we should make our decisions based on existing information and the current estimate of expected net benefit, there is always a chance that another alternative would have had a higher net benefit once our current uncertainties are resolved.[213] If the recommended course of action turns out to be wrong, there will be costs in terms of health benefits and resources forgone. The expected cost of uncertainty, known as expected value of perfect information (EVPI), is determined jointly by the probability that a recommended course of action based on current evidence is wrong, and the consequences of wrong decision.[213] EVPI represent the maximum that the healthcare system should be willing to pay to obtain additional evidence to inform the same decision in the future. In other words, EVPI puts an upper bound on the value of conducting future research.[213] More research on model parameters is justified if the expected benefit to future patients (estimated as the product of EVPI per patient and the population that is expected to benefit from future research) exceeds the cost of proposed research.[214] To examine the contribution of different parameters to the overall uncertainty and identify the type of additional evidence most valuable, I calculated partial EVPI for 4 sets of parameters: costs, efficacy of decompressive craniectomy and barbiturate therapy

at 6 months following injury, natural history of severe TBI patients who suffer refractory intracranial hypertension after the first 6 months, and quality-of-life measures.

Results

Costs and Health Effects

The average gain, over 10,000 samples (each sample represents 1000 trials), in quality-adjusted life expectancy with decompressive craniectomy relative to barbiturate coma was 1.5 QALY (i.e., 18.5 quality-adjusted life months). However, decompressive craniectomy increased the average lifetime costs by $14,784. The ICER, comparing decompressive craniectomy with barbiturate coma, was $9,565/QALY gained (Table 3.5).

Decompressive craniectomy resulted in greater quality-adjusted life expectancy in 86% of simulations (Figure 3.4). Decompressive craniectomy was more cost-effective than barbiturate coma in 78% of cases when the willingness-to-pay threshold was set at $50,000/QALY, and 82% of cases with a threshold of $100,000/QALY.

A cost-effectiveness acceptability curve shows my model prediction of the most cost-effective treatment option at different willingness-to-pay thresholds (Figure

3.5). Decompressive craniectomy was the most cost-effective strategy in the majority of cases at willingness-to-pay thresholds greater than $6,000/QALY.

Sensitivity Analyses

Variations in the mean age of simulated patients revealed that decompressive craniectomy was associated with gains in quality-adjusted life expectancy compared to barbiturate coma as the mean age for simulated patients increased, but at higher ICER values (Figure 3.6). At a mean age of >65 years, the ICER for decompressive craniectomy, relative to barbiturate coma, exceeded $50,000/QALY.

Assuming hypotension can be avoided in all patients, including patients who received barbiturate therapy, decompressive craniectomy remained more attractive but at a higher ICER ($16,236/QALY). When the analysis was repeated under the assumption that life expectancy of all survivors after 5-7 years post-injury is reduced regardless of their GOS category, results were unchanged (ICER for decompressive craniectomy, $9,576/QALY). The magnitude of ICER for decompressive craniectomy, relative to barbiturate coma, was sensitive to replacing the nationwide average cost estimate of skilled nursing care in the model with state-specific estimates. For example, in the state of New York in which care at a nursing home costs $275.70/day as per Medicaid[206], the ICER for decompressive craniectomy was $15,252/QALY. In contrast, the ICER for decompressive craniectomy in Texas was $6,125/QALY, where the reported cost of nursing care is $147.4/day.[206] At 5% discount rate, the ICER for decompressive craniectomy was $9,693/QALY.

Value of Information Analyses

The total EVPI for further research was $14,982/patient at a willingness-to-pay threshold of $50,000/QALY. Partial EVPI calculations showed that the value of perfect information about individual parameters varied depending on which subgroup of parameters was evaluated. At a willingness-to-pay threshold of $50,000/QALY, further research on natural history of severe TBI patients with refractory intracranial hypertension appears to be most valuable (Figure 3.7).

Discussion

This cost-utility analysis showed that decompressive craniectomy for the treatment of refractory intracranial hypertension following severe TBI resulted, on average, in greater quality-adjusted life expectancy relative to treatment with barbiturate coma. However, one would have to spend a mean of $9,565 to gain an additional year of healthy life compared to barbiturate coma. At the commonly cited $50,000/QALY willingness-to-pay threshold, decompressive craniectomy would be considered economically attractive. These findings were robust in sensitivity analyses in which several model assumptions were tested.

Decompressive craniectomy in older patients was still associated with QALY gains, but the ICER value increased to $197,906/QALY for a mean age of 85 years. This ICER value, although high and traditionally unattractive, may be within the range in which other considerations, such as ethics and age-equity in treatment decision-

making, persuade a decision maker to adopt a relatively inefficient treatment.[215] Furthermore, policy makers may consider ICERs contextually.[215] Nevertheless, I recognize that the concept of population-specific willingness-to-pay thresholds remains debatable.

The majority of patients who die from TBI do so because of uncontrolled intracranial hypertension within the first few days following injury.[144,145] The most commonly used treatment strategies when first-line medical therapies fail are decompressive craniectomy and high-dose barbiturate therapy.[107,124,181] In spite of being the most commonly administered treatments for this condition, there are no published randomized trials comparing the two strategies. A recent trial compared decompressive craniectomy with medical care, which in some cases may or may not have included barbiturate coma, and found that decompressive craniectomy was associated with a greater risk of unfavorable outcome at 6 months.[129] However, critics of this trial have highlighted unbalanced treatment groups, considerable variability in medical treatments for the control group, high cross-over rate to the surgical arm, and relatively short follow-up time as arguments against the widespread application of the study findings.[130,131] Another trial compared barbiturates to other medical options for the management of refractory intracranial hypertension following TBI.[132] The trial showed that barbiturates were more effective at controlling high ICP, and responders were more likely to survive[132] However, the impact of barbiturates on the functional outcome of survivors was not examined in that trial. Given the substantial uncertainty in this area, economic evaluation methods can help to provide some guidance to clinicians and policy

makers. Ho and colleagues conducted a cost-utility analysis to compare decompressive craniectomy as a life saving procedure for patients with severe TBI versus withdrawal of life support.[216] Their analysis concluded that craniectomy might not be economically attractive if the willingness-to-pay threshold is equal or below US $100,000.[216] However, the clinical effectiveness data were derived from a single retrospective case series that included individuals with bilaterally fixed and dilated pupils who were unlikely to benefit from any therapy. In addition, the investigators assumed that functional outcome is fixed after 18 months post-injury, which is contrary to previous longitudinal studies of TBI functional outcome.[193,217]

This analysis has a number of advantages. First, I studied the two most common contemporary treatments for refractory intracranial hypertension. Second, I employed a more complex model structure that more closely reflected patients' lifetime clinical course. Third, using data from prospective cohort studies, I avoided making assumptions regarding patients' functional outcome trajectory and assumptions about the proportion of patients who require skilled nursing care several years following the injury; both represent major determinants of long-term costs in TBI economic evaluations.[202] Fourth, I derived clinical efficacy estimates from randomized trials. Finally, I examined the impact of uncertainty surrounding model parameters in two-dimensional simulations using distributions of possible values rather than point estimates.

The value of information analysis provided important insights. It highlighted the significance of undertaking future studies to better characterize the natural history

of severe TBI patients who suffer refractory intracranial hypertension, the efficacy of decompressive craniectomy and barbiturate therapy, and the costs of care and quality of life of these patients. In the United States, an estimated 1.37 million people visit the emergency department because of acute TBI annually.[218] If 10% of patients who suffer from severe TBI (137,000 patients or 10% of all TBIs [82]) develop refractory intracranial hypertension[107,181], "perfect" information about model parameters would be worth in excess of $205 million over 1 year (assuming information are used for only 1 year), or more than $960 million over 5 years (discounting at 3% per year). Furthermore, the partial EVPI analyses suggested that the individual contribution of model parameters to the overall uncertainty, and therefore, the value of funding future research vary depending on the type of additional evidence sought. At a willingness-to-pay threshold of $50,000/QALY, further evidence on the natural history of severe TBI patients with refractory intracranial hypertension would be most valuable.

My study has several limitations, including the paucity of high-quality studies to derive estimates for several parameters in the model. The model results may need revision as future rigorous investigations refine these estimates. I did not consider all possible treatment options, such as hypothermia, for refractory intracranial hypertension. However, this analysis was intended to compare commonly used treatment modalities in current practice.[107,124,181] Furthermore, only these two treatment options were recommended for the management of refractory intracranial hypertension following TBI by the Brain Trauma Foundation guidelines.[35,128] Future analyses will be required to explore the economical

attractiveness of additional options as evidence in support of the adoption of other treatment strategies emerges. Because cost parameterization data were derived from US studies, the results may not be generalizable to other countries, particularly since healthcare costs can vary considerably across different healthcare systems.

In treating refractory intracranial hypertension following TBI, decompressive craniectomy is superior to barbiturate coma in terms of fiscal costs and health gains, based on available evidence. The relative economic advantage might be less apparent among older patients. Further research to address current uncertainties, particularly on the long-term natural history of TBI patients with refractory intracranial hypertension, is needed to make more informed treatment decisions.

CHAPTER 4: Tracheostomy Timing in Traumatic Brain Injury

The purpose of this chapter is to:

1. Characterize the timing of tracheostomy among TBI patients.
2. Examine the differences in the characteristics of patients who undergo early and late tracheostomy.
3. Examine the relationship between tracheostomy timing and the duration of mechanical ventilation, ICU and hospital length of stay among TBI patients.
4. Introduce general methods to address confounding by indication and immortal time bias that can be applied to other processes of care among TBI population.

Acknowledgment: parts of this chapter were reprinted from: Alali AS, Scales DC, Fowler RA, et al. Tracheostomy timing in traumatic brain injury: A propensity-matched cohort study. *The journal of trauma and acute care surgery.* Jan 2014;76(1):70-78, with permission from Lippincott Williams & Wilkins. I also would like to acknowledge my co-authors: Damon C. Scales, Robert A. Fowler, Todd G. Mainprize, Joel G. Ray, Alexander Kiss, Charles de Mestral and Avery B. Nathens for granting permission to reproduce this material.

Summary

The optimal timing of tracheostomy in patients with severe TBI is controversial; observational studies have been challenged through confounding by indication and interventional studies have rarely enrolled patients with isolated TBI.

I examined a cohort of adults with isolated TBI who underwent tracheostomy within one of 135 participating centers in the American College of Surgeons Trauma Quality Improvement Program, during 2009-2011. Patients were classified as having undergone early (≤8 days) or late tracheostomy (>8 days). Outcomes were compared between propensity score-matched groups to reduce confounding by indication. In sensitivity analyses, I used time-dependent proportional hazard regression to address immortal time bias, and assessed the association between hospital early tracheostomy rate and patients' outcome at the hospital-level.

From 1,811 patients, a well-balanced propensity-matched cohort of 1,154 patients was defined. After matching, early tracheostomy was associated with fewer mechanical ventilation days (median 10 vs. 16 days; rate ratio 0.70; 95% confidence interval: 0.66-0.75), shorter ICU stay (median 13 vs. 19 days; rate ratio 0.70; 95% confidence interval 0.66-0.75), shorter hospital length of stay (median 20 vs. 27 days; rate ratio 0.80; 95% confidence interval 0.74-0.86), and lower odds of pneumonia (41.7% vs. 52.7%; odds ratio 0.64; 95% confidence interval 0.51-0.80), deep venous thrombosis (8.2% vs. 14.4%; odds ratio 0.53; 95% confidence interval 0.37-0.78) and decubitus ulcer (4.0% vs. 8.9%; odds ratio 0.43; 95% confidence interval 0.26-0.71), but no significant difference in pulmonary embolism (1.8% vs. 3.3%; odds ratio 0.52; 95% confidence interval 0.24-1.10). Hospital mortality was similar between both groups (8.4% vs. 6.8%; odds ratio 1.25, 95% confidence interval 0.80-1.96). Results were consistent using several alternative analytic methods.

In this observational study, early tracheostomy was associated with a shorter duration of mechanical ventilation, ICU stay and hospital stay; but not hospital mortality. Early tracheostomy may represent a mechanism to reduce in-hospital morbidity for patients with TBI.

Background

Patients suffering severe TBI often require mechanical ventilation in ICUs as a component of their initial post-injury care. While in the ICU, they commonly undergo tracheostomy to ensure a patent airway when level of consciousness remains persistently depressed and thereby facilitate liberation from mechanical ventilation.[109,111] However, there is substantial variability in the rate of tracheostomy and its timing among different institutions.[219-223]

The foreseen benefits of performing early tracheostomy for patients undergoing prolonged mechanical ventilation include improved patient comfort due to reduced oropharyngeal irritation;[224] improved pulmonary toilet that might also accelerate liberation from mechanical ventilation; and, a possible resultant decrease in the risk of pneumonia and ventilator-induced lung injury.[225,226] The concern with routinely performing early tracheostomy is that some patients might be unnecessarily exposed to potential complications, including bleeding, acute and chronic airway injury.[110,111]

The benefit of early tracheostomy in the general medical-surgical critically ill patients remains unproven despite multiple randomized controlled trials.[227,110,136-140] However, isolated TBI patients represent a unique subpopulation. In contrast to other critically ill patients, isolated TBI patients often require little or no assistance from mechanical ventilators and might be liberated more promptly from the ventilator once the airway is secured with a tracheostomy.[110,111] Therefore, it is important to study tracheostomy timing in isolated TBI separately.

In this context, I conducted an observational cohort study using data derived from the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) to ascertain whether early tracheostomy, compared to late tracheostomy, in patients with isolated TBI is associated with a shorter duration of mechanical ventilation, and shorter ICU and hospital length of stay.

Methods

Study Design

I completed a retrospective cohort study of patients admitted to hospital with TBI who received tracheostomy during their acute hospital stay as recorded by the ACS TQIP. Outcomes were compared between patients who underwent tracheostomy within 8 days of admission and patients whose tracheostomies were performed later. The study was approved by the research ethics board of Sunnybrook Health Sciences Center, Toronto, Ontario, Canada.

Data Source

TQIP was established to allow an opportunity for trauma centers to compare their process of care and outcomes with other centers.[161] The program includes more than 150 level I and II trauma centers in the United States and Canada. More than 100 patient and hospital variables are recorded including patient demographics, premorbid conditions, injury type, mechanism and severity, prehospital and emergency room physiological variables, in-hospital procedures, and outcome information, including in-hospital morbidity and mortality.[161] The reliability of the data is ensured using intensive training mechanisms for data abstractors and interrater reliability audits of participating sites.[160,161] Inclusion into TQIP requires at least one valid trauma International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code in the range of 800–959, excluding late effects of trauma (905–909).[161]

Cohort

I identified patients aged ≥16 years who were admitted between January 1, 2009 and December 31, 2011 to a TQIP hospital with Head Abbreviated Injury Score (AIS) ≥3. The study only included patients who received tracheostomy during their acute hospital stay. To ensure homogeneity of the cohort, exclusion criteria were: severe injuries (AIS >2) in any other body region; penetrating TBI; and prior advanced directives to withhold life-sustaining interventions.

Exposure

Patients undergoing tracheostomy were identified by the presence of one of the following ICD-9-CM procedure codes: 31.1 (temporary tracheostomy), 31.21 (mediastinal tracheostomy) or 31.29 (other permanent tracheostomy). Tracheostomy timing was defined as the number of days between hospital admission and the tracheostomy procedure, and was categorized into two periods: 'early' (if performed within 8 days after admission) and 'late' (if performed on or after the 9th day of admission). I chose this cut-off point to define the exposure to ensure consistency with recently published randomized trials and because the median time to tracheostomy in this cohort was 9 days.[135] I also explored other thresholds by dividing tracheostomy timing into quartiles in a sensitivity analysis. Only the first record of tracheostomy was analyzed for each patient during the index hospitalization.

Outcomes

The primary outcome was duration of mechanical ventilation in days. The following secondary outcomes were analyzed: The secondary outcomes of the study were: 1) ICU length of stay in days; 2) hospital length of stay in days; 3) in-hospital mortality; 4) hospital-acquired pneumonia, which was defined as the presence of clinical symptoms and/or signs in addition to radiological and/or microbiologic evidence of pneumonia; 5) deep venous thrombosis, which was defined as evidence of venous thrombosis in the lower extremities that was confirmed by venogram or ultrasound and treated with anticoagulation and/or placement of a vena cava filter; 6) pulmonary embolism, which was defined as a high probability ventilation-perfusion

scan, positive CT or conventional pulmonary angiogram for pulmonary embolism; 6) decubitus ulcer, which was defined as a pressure sore resulting from pressure exerted on the skin, soft tissue, muscle, or bone by the weight of an individual against a surface beneath.[228]

Covariates

The following patient-level covariates were considered for inclusion into the adjusted analyses: age, gender, race, comorbid illnesses, injury mechanism and severity (as measured by Head AIS), Glasgow Coma Scale (GCS) motor score, type of intracranial lesion, presence of systolic hypotension on admission, whether a neurosurgical procedure (craniotomy and intracranial pressure monitor insertion) was performed, and insurance status. To identify acute intracranial lesions, I used AIS predot codes (1998 version) that reflect injuries to the intracranial structures (Table 1.4). To characterize the hospital environment, which may influence the relation between process of care and outcome, I classified centers based on the following factors: volume of severe TBI patients per hospital during the study period (divided into quartiles); teaching status; number of hospital beds; hospital type (nonprofit versus for-profit); and, ACS or state trauma center designation level (level I versus II).

Statistical Analysis

I calculated standardized differences to compare baseline characteristics between patients who received early versus late tracheostomy. Standardized differences

represent the mean difference as a percentage of the standard deviation.[162] To estimate these, differences between groups are divided by the pooled standard deviation of the two groups.[162,163] The advantage of standardized differences is that they are not as sensitive to sample size as traditional tests and provides a sense of the relative magnitude of differences.[162] Standardized differences of greater than 0.1 are typically considered meaningful.[162]

I chose propensity score matching as the primary analytic method for a number of reasons. Propensity score methods allow simultaneous control for confounding by several variables in situations where conventional multivariable models might not be appropriate, owing to the rareness of outcomes.[229] Because 10 events per covariate is typically considered to be a minimum requirement for stable estimates in multivariable models, propensity score methods combining multiple covariates into a single score are especially desirable if the outcome is rare. A simulation study by Cepeda et al. comparing propensity score methods with multivariable outcome models concluded that propensity score methods performed better in situations with less than 8 outcomes per covariate.[230] In my study, many outcome measures were rare (e.g. mortality and pulmonary embolism) relative to the large number of potential confounder. Another advantage of propensity score methods over conventional multivariable models is that one can explicitly determine the degree to which one has balanced measured characteristics between exposure and control subjects.[231] By matching subjects based on their probability to receive treatment, propensity score matching has an intuitive potential to match only patients in whom there was more decision uncertainty regarding assignment to the exposure (i.e.

early tracheostomy) vs. the control (i.e. early tracheostomy).[232] In addition, a previous comparative study of propensity score methods by Austin and Mamdani have suggested that matching results in the comparison of exposure and control subjects who are more similar to each other than does other propensity score methods.[231]

Propensity scores to estimate the probability, based on individual and hospital characteristics, that patients would be selected to undergo early tracheostomy were developed using a logistic regression model. I used structured iterative approach to refine this logistic regression model to achieve balance of covariates within the matched pairs as described below.

Propensity score matching was performed using a 1-to-1 matching technique without replacement.[233] The procedure sorted all patients according to the propensity scores and matched each exposed (i.e. underwent early tracheostomy) patient to an unexposed (i.e. underwent late tracheostomy) patient within 0.2 standard deviation of the logit of the propensity score.[234] If multiple unexposed controls matched to an exposed patient, then one control was randomly selected. After a patient was matched, that match was not reconsidered. The covariate balance after matching was assessed by calculating the standardized difference of the mean or proportion for each covariate, with a standardized difference of <0.1 indicating sufficient balance.[235] Within the propensity-matched cohort, the statistical significance of the differences in outcomes was assessed using McNemar's test to compare proportions and Wilcoxon signed-rank test to compare

distributions.[232,235] Taking into account the matched nature of the data, I calculated a rate ratio and 95% confidence interval assuming a negative binomial distribution for each of the following outcomes: mechanical ventilation days, ICU and hospital length of stay.[236] Odds ratios and 95% confidence intervals were estimated for binary outcomes.

Subgroup Analyses

Multiple patient subgroups were defined according to age, gender, injury mechanism and severity, comorbid illnesses, type of intracranial injury and insurance status. I adjusted for baseline differences in each of the patient subgroups using negative binomial regression model that contains the same propensity score calculated in the primary analysis.

Sensitivity Analyses

Excluding In-hospital Deaths

Patients who die early during hospital stay are more likely to have shorter mechanical ventilation, ICU and hospital stay, and fewer in-hospital complications. To explore this potential source of bias, the data were re-analyzed after excluding patients who died in the hospital, at any point, using propensity score matching as in the primary analysis.

Proportional Hazards Regression with Time-dependent Exposure

Using the entire cohort, I considered tracheostomy timing as a time dependent

exposure to account for the potential immortal time bias (i.e. survivor treatment bias). Immortal time refers to a period of follow-up during which, because of exposure definition, the study outcome cannot occur.[237] Using proportional hazard regression with time-dependent exposure, a patient was entered into the model as a step function starting only on the day of the tracheostomy procedure but the hazard of event (e.g. liberation from mechanical ventilation or discharge) was indexed to time since the admission.[238-240] Therefore, a patient was defined as unexposed until the day of the tracheostomy procedure and exposed afterwards. This approach ensured that estimated hazard ratios between exposure and control groups were not distorted by comparisons before the day of tracheostomy procedure.[240] In addition, this model adjusted for the following covariates: age, gender, race, comorbid illnesses, injury mechanism and severity (defined using AIS score for body region Head), GCS motor score, presence of hypotension on admission, type of intracranial lesion, whether a neurosurgical procedure (craniotomy and intracranial pressure monitor insertion) was performed, and insurance status. To account for potential correlation between TBI patients within hospitals, I used a sandwich-type robust variance estimator.[241]

Hospital-Level Analysis of the Relationship Between Tracheostomy Timing and Outcome

It is plausible that residual confounding by indication might create a spurious association between timing of tracheostomy and outcome at the patient level. To attempt to overcome this limitation, I asked a second question: do centers with high

rates of early tracheostomy have shorter duration of mechanical ventilation and length of stay? To accomplish this objective, I divided hospitals into quartiles based on their specific rate of early tracheostomy utilization among TBI patients. Then, I evaluated this factor as a determinant of mechanical ventilation days and ICU and hospital length of stay for their TBI population undergoing tracheostomy (regardless of timing) after adjusting for patient- and hospital-level characteristics. The covariates included in the adjusted analysis were similar to those included in the propensity score model.

Tracheostomy Timing Divided into Quartiles

I repeated the analysis after dividing the tracheostomy timing into quartiles instead of two exposure groups: <6 days, 6-<9 days, 9-<12 days and ≥12 days. Using generalized estimating equations to account for clustering at hospital level, adjusted analyses included the following covariates: age, gender, race, comorbid illnesses, injury mechanism and severity (defined using AIS score for body region Head), GCS motor score, presence of hypotension on admission, type of intracranial lesion, whether a neurosurgical procedure (craniotomy and intracranial pressure monitor insertion) was performed, and insurance status.

Influence of Unmeasured Confounding

Finally, I explored the impact of possible unmeasured residual confounding to assess whether the observed differences in the primary outcome (i.e. mechanical ventilation days) could be fully explained by an unmeasured confounder.[242]

All analyses were performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina), and statistical significance was defined as a two-tailed P value <0.05.

Results

Characteristics of Study Cohort

The study cohort consisted of 1,811 adults with isolated TBI who underwent tracheostomy at 135 level I and II trauma centers participating in ACS TQIP. The median time to tracheostomy was 9 days (interquartile range: 6-12 days) from admission. Table 4.1 shows the baseline characteristics of the study patients. The early tracheostomy ($\leq$8 days; median: 6 days; interquartile range: 4-7 days) patients were younger, had a lower comorbidity burden, suffered more severe TBIs, were more likely to have commercial insurance, and were treated at hospitals with a higher volume of severe TBI patients than the patients who received late tracheostomy (>8 days; median: 12 days; interquartile range: 10-15 days). Conversely, patients who received late tracheostomy were more likely to experience subdural hematomas and fall-related injuries. There was no significant difference between the two groups in the frequency of craniotomy or ICP monitoring.

Propensity-Matched Cohort

Propensity-score matching generated 571 distinct pairs (N=1,142). Within the matched cohort, all the individual and hospital characteristics were well balanced (Tables 4.2). After matching, early tracheostomy was associated with fewer mechanical ventilation days (rate ratio: 0.70, 95% confidence interval 0.66-0.75), shorter ICU stay (rate ratio: 0.70, 95% confidence interval 0.66-0.75) and shorter hospital length of stay (rate ratio: 0.80, 95% confidence interval: 0.74-0.86) (Table 4.3). In other words, early tracheostomy patients had 30% fewer mechanical ventilation days, 30% shorter ICU stay and 20% shorter overall hospital stay, compared with late tracheostomy patients. Early tracheostomy was also associated with significantly lower odds of pneumonia, deep venous thrombosis and decubitus ulcer, but no significant difference was found in the odds of pulmonary embolism or in-hospital mortality (Table 4.4).

Among the early tracheostomy group, the unmatched patients had a higher probability of receiving early tracheostomy compared with the matched patients (mean propensity score 0.76 vs. 0.51, $p<0.0001$), which may reflect lower decision uncertainty in patient selection for early tracheostomy. In addition, the unmatched early tracheostomy patients had similar (median mechanical ventilation days: 10 vs. 10 days, respectively, $p=0.37$; median ICU stay: 13 days vs. 13 days, respectively, $p=0.69$) or more favorable outcomes compared with matched patients (median hospital stay: 18 days vs. 20 days, respectively, $p=0.02$).

Subgroup analyses

After adjustment, early tracheostomy was associated with fewer mechanical

ventilation days across almost all patient subgroups, although occasionally confidence intervals overlapped the null effect (Figure 4.1). Late tracheostomy was not superior in any of the patient subgroups.

Sensitivity Analyses

Excluding In-hospital Deaths

After excluding patients who died in the hospital at any point, the cohort was reduced to 1,668 patients. Applying the same propensity-score model and matching algorithm as for the primary analysis resulted in 516 well-balanced matched pairs. The results for this analysis are similar to the primary analysis (Tables 4.5 and 4.6). The only difference was that the association between early tracheostomy and lower odds of pulmonary embolism became statistically significant (p=0.02).

Proportional Hazards Regression with Time-dependent Exposure

Using the entire cohort, I repeated the analysis using multivariate proportional hazards regression considering tracheostomy timing as a time-dependent variable to account for possible immortal time bias. Early tracheostomy was found to be associated with a higher likelihood (i.e. hazards) of liberation from mechanical ventilation, discharge from the ICU and discharge from the hospital (Table 4.7).

Hospital-Level Analysis of the Relationship Between Tracheostomy Timing and Outcome

When the 135 hospitals were stratified into quartiles based on their rate of early

tracheostomy use, there was considerable inter-hospital variation in early tracheostomy with a median utilization rate of 50% (interquartile range: 30–64%). This large variation was accompanied by differences in patient and hospital characteristics across the four quartiles (Table 4.8). In quartile 4 (highest early tracheostomy rate), patients had more severe injuries (as measured by GCS score) but had similar distribution of comorbid illnesses. In addition, hospitals with the highest volume of TBI patients tend to be in quartile 3 and 4.

Compared to the quartile with the lowest early tracheostomy rate (quartile 1), the adjusted rate ratio of mechanical ventilation days was 0.67 (95% confidence interval: 0.60-0.74) for quartile 4, 0.79 (95% confidence interval 0.69-0.89) for quartile 3 and 0.81 (95% confidence interval 0.73-0.91) for quartile 2. Similar dose-response trends were noticed with ICU and hospital length of stay (Table 4.9).

Tracheostomy Timing Divided into Quartiles

Results were consistent after dividing tracheostomy timing into quartiles instead of two exposure groups (Table 4.10).

Influence of Unmeasured Confounding

From the time-dependent proportional hazards model, the adjusted hazard ratio for liberation from mechanical ventilation associated with early versus late tracheostomy was 2.04 (95% confidence interval: 1.83-2.27). Figure 4.2 summarizes the method used to assess whether an unmeasured binary confounder would account for a hazard ratio of this magnitude.[243] For example, if the prevalence of an

unmeasured confounder was 10% in the early tracheostomy group (curved blue line) and 60%, 75% or 90% in the late tracheostomy group, then the confounder itself could explain the observed difference in the likelihood of liberation from mechanical ventilation between both groups only if it decreased the likelihood (hazard) of liberation from mechanical ventilation by 93% (hazard ratio: 0.07), 73% (hazard ratio: 0.27) and 60% (hazard ratio 0.4), respectively.

Discussion

In this observational study, I found that early tracheostomy was associated with reduced duration of mechanical ventilation and shorter ICU and hospital stay. The findings were consistent when I used multiple analytical approaches to examine these relations. The analysis also suggests that early tracheostomy is associated with lower risks of pneumonia, deep venous thrombosis and decubitus ulcer, with a trend toward a lower risk of pulmonary embolism. However, this study did not find an association between tracheostomy timing and in-hospital mortality in patients with isolated TBI.

The most common indication for tracheostomy in the ICU is to provide long-term airway access for prolonged mechanical ventilation and to allow a conduit for suctioning.[227,244] Performing early tracheostomy in the critically ill is postulated as a mechanism to improve clearance of respiratory secretions, which might accelerate liberation from mechanical ventilation, and thereby reduce the risk of pneumonia

and ventilator-induced lung injury.[245,246] Earlier liberation from mechanical ventilation may also promote earlier ambulation and hence lower the risk of thromboembolism and decubitus ulcers.[239,247,248] Nevertheless, previous studies provide little guidance regarding optimal tracheostomy timing. A systematic review of several randomized trials showed no evidence of benefit for early tracheostomy in the general medical-surgical critically ill patients, and a marked excess in the procedure rate among patients randomized to the early tracheostomy.[135,227] However, the indications for mechanical ventilation and the underlying lung mechanics are variable in different patient subgroups. In isolated TBI patients, reduced consciousness and depressed protective airway reflexes cause airway protection to be the primary indication for endotracheal intubation with little need for support from the ventilator to achieve adequate gas exchange.[109,110] Hence, faster liberation of these patients from mechanical ventilators could potentially be achieved once the airway is secured with a tracheostomy tube.

Previous studies of tracheostomy timing in TBI have not shown consistent or conclusive results.[110,136-140] The findings presented herein agree with previous studies that showed a significant association between early tracheostomy and shorter mechanical ventilation and ICU stay in addition to reduced risk of pneumonia in TBI patients,[137,140] but contrast with others that did not reveal such significant associations, found no effect on overall hospital stay and/or showed higher mortality with early tracheostomy.[110,136,138,139] However, prior studies suffered from a number of limitations, which may explain their contradictory results. In addition to the small sample size in the majority of the previous studies,

none of the studies was restricted to patients with isolated TBI who have no significant multisystem injuries.[110,136-140] Multisystem trauma might increase the risk for long-term ventilator dependency and alter the unique potential advantage of early tracheostomy in TBI patients.[141,142] Moreover, the surprising finding of higher mortality with early tracheostomy in some of the previous studies suggests that residual confounding may have significantly biased their results.

In addition to the focused primary diagnosis of this cohort, the strengths of this study include very large sample size and the use of multiple analytical techniques to address the potential biases that commonly confound tracheostomy timing studies; most importantly confounding by indication and immortal time bias. Such biases are commonly ignored in these studies. In my primary analysis, I used propensity-score matching on many measured individual- and hospital-level characteristics to obtain a well-balanced cohort and minimize confounding by indication. Immortal time bias, which is also known as survivor-treatment bias, can confound such studies because the outcome of interest (i.e. liberation from mechanical ventilation, discharge from ICU or death) could not occur before a certain time in the late tracheostomy group because of the exposure definition.[240] To account for this bias and address the censoring of outcomes by mortality, I used proportional hazards regression considering tracheostomy timing as a time-dependent exposure.[238-240] Additionally, clustering of TBI management strategies at different hospitals could lead to a clustering of the patient outcomes. In my proportional hazards model, I accounted for potential correlation among patients within hospitals.

Several limitations should be considered when interpreting the results of this study, including the inability to precisely ascertain certain secondary outcomes, such as pneumonia and deep venous thrombosis. However, there is no compelling reason to believe that information on these outcomes was gathered differently between the exposure and control groups. Furthermore, non-differential misclassification tends to bias point estimates towards finding no difference, leading to more conservative results.[249]

It is noteworthy that statistical methods cannot adjust for unmeasured confounding factors. The database I used in this study did not include information on certain factors that may influence the decision to perform tracheostomy, such as physician judgment, changes in physiological variables, patient progress during his/her hospital stay and the patient's or patient family's approach to life-sustaining interventions. Therefore, and given the possibility of similar distributions of unmeasured confounding among different hospitals, I repeated the analysis after changing the exposure definition to be the hospital-specific rate of early tracheostomy use. This approach provided similar results to the individual-level analysis. I also explored the impact of a hypothetical unmeasured confounder in a sensitivity analysis. The analysis suggests that the observed difference in outcome between the two groups could be accounted for by a single unmeasured variable, or multiple confounding variables acting in concert, only if this confounder (e.g. frailty) was approximately 2-10 times more prevalent in the control group and this confounder decreased the likelihood of liberation from mechanical ventilation by

93-54%, respectively. Not only such hypothetical confounder of this magnitude appears implausible in this cohort, but they could also increase the difference.

Limited by the database, I could not capture patients who were potential candidates for tracheostomy but were successfully liberated from mechanical ventilation without ever undergoing this procedure. This study provides guidance on the timing of the tracheostomy procedure in TBI patients rather than patient selection. Therefore, the findings of my analysis suggest that early tracheostomy might reduce in-hospital morbidity and accelerate ambulation only among those who already have indications for this procedure.

Due to the low number of in-hospital deaths in this cohort, I cannot conclusively exclude a mortality difference. Future studies to address this question will likely require a much larger sample size to detect whether a small survival advantage for early tracheostomy may exist in this patient population. Further studies should also consider examining important long-term consequences of tracheostomy, other than its impact on survival, including risk of chronic tracheal stenosis, patient- and family-centered endpoints, such as cosmetic outcome and communicative ability, and preference-based quality of life measures.

In this observational study, early tracheostomy was associated with a shorter duration of mechanical ventilation, ICU stay and hospital stay; but not hospital mortality. Early tracheostomy may represent a mechanism to reduce certain elements of in-hospital morbidity for patients with TBI.

CHAPTER 5: Conclusions

The purpose of this chapter is to:

1. Summarize the findings of the three studies comprising the thesis.
2. Discuss the limitations of the studies.
3. Outline the implications of the thesis findings for clinicians and policy makers.
4. Discuss suggestions for future research involving severe TBI patients.

Summary of Findings

The three studies described herein have demonstrated how a variety of health services research methods and analytical approaches can be used to understand the relationship between processes of ICU care and outcome of severe TBI patients. Furthermore, the common conceptual model underlying these studies may serve as a framework for future studies involving critically ill TBI patients.

First, I showed a strong association between invasive ICP monitoring and a lower risk of death following severe TBI. This finding was consistent when I examined the effectiveness of this technology at either the patient or the hospital level. In addition, there appeared to be a dose-response relationship, with higher rates of ICP monitoring utilization associated with lower risk of hospital-specific TBI mortality. Further, this study has showed how multilevel modeling techniques can be used to

provide important insights into the drivers of variability in TBI outcome. Using these techniques, I demonstrated that the contributions of ICP monitoring use and the volume of TBI patients per hospital to the observed inter-hospital variability in TBI mortality are modest, and a large proportion of such variability remains unexplained.

Second, I evaluated whether decompressive craniectomy or barbiturate coma provides better value, in terms of both health effects and costs, for the management of refractory intracranial hypertension following severe TBI. I concluded that, for this indication, decompressive craniectomy results, on average, in greater quality-adjusted life expectancy relative to barbiturate coma, but at higher costs. I showed that at the commonly cited $50,000/QALY willingness-to-pay threshold, decompressive craniectomy would be considered economically attractive among patients aged 65 years or younger from the perspective of a healthcare payer. In this study, I demonstrated that economic evaluation methods provide a unique opportunity to identify the optimal strategy among alternative courses of action for the management of severe TBI, where uncertainty is common and the consequential health and economic burden on both the patients and the healthcare system is substantial. Although the decision analytical model presented herein was constructed to address a specific question, its general structure may serve as a framework for other decision problems involving the management of severe TBI patients. Further, I demonstrated that microsimulation is a useful modeling tool for TBI economic evaluations: it allows for individual patient variability with respect to attributes, such as demographics and injury severity, that affect long-term TBI

outcome, such that it provides a more accurate depiction of the complex TBI patients' lifetime clinical course than cohort simulation. I also showed that value of information analytical methodology can be used to identify the most valuable type of additional evidence and prioritize TBI research funding accordingly.

Third, I studied the relationship between the timing of a common process of care for critically ill TBI patients, tracheostomy, and a number of clinical outcomes. I showed that early tracheostomy in TBI patients is associated with reduced duration of mechanical ventilation, shorter ICU and hospital stay, and lower risk of pneumonia, without a survival advantage. I concluded that early tracheostomy might be a mechanism to reduce hospital morbidity for TBI patients. In this study, I demonstrated the importance of using multiple sophisticated analytical techniques, such as propensity-score matching and time-dependent proportional hazards regression, in examining the impact of the timing of a process of care on TBI outcomes, to address confounding by indication and immortal time bias. This study also questioned the feasibility of conducting randomized trials to test whether a small survival advantage for early tracheostomy exists in the TBI population.

Limitations

An important limitation of the research presented here is the lack of detailed information about certain clinical nuances. These deficiencies render the studies' results vulnerable to bias due to unmeasured confounding. Therefore, despite the

use of multiple analytical approaches and sophisticated statistical techniques, I cannot rule out with certainty that the reported associations are due to random chance rather than true treatment effects.

A second limitation of my thesis is that the lack of detailed information on pathophysiological pathways. To better understand the reported associations, further basic laboratory research and prospective observational studies that collect data on genetic, biochemical and physiological variables are needed to further elucidate the underlying biological processes and help ascertain causal relationships. Nonetheless, health services research methods, although they cannot solely establish causal relationships, are valuable to generate hypotheses, understand the epidemiology of disease, and complement laboratory research and clinical trials through testing the translation of their findings to real clinical practice settings.

A third limitation is the focus on in-hospital mortality and morbidity in certain parts of the thesis. Ideally, the occurrence of complications after discharge from the hospital, especially death, should be captured in ICU studies of the relationship between process of care and outcome, to understand the late effects of disease and treatment. However, prior studies of the natural history of hospitalized TBI patients have suggested that TBI-attributable deaths after hospital discharge are uncommon.[180] This observation suggests that short-term endpoints are more efficient, although not ideal, for detecting treatment differences in clinical studies involving severe TBI patients.

A fourth limitation of my thesis is the lack of data on the relationship between certain processes of care in the ICU and important outcome measures other than mortality, such as functional outcome and health-related quality of life. These endpoints are highly relevant in the severe TBI population, where severe disability and poor quality of life are common consequences of injury. Furthermore, interventions that prolong the survival of TBI patients may negatively influence their quality of life. Examining these relationships should be the focus of additional research.

Finally, because the data in my thesis were derived from verified level I and II trauma centers in the United States, the generalizability of findings to other settings might be limited. That is, the reported associations herein may not exist among patients treated at other facilities in the same healthcare system, or patients treated at similar facilities in a different system. The limited generalizability might stem from differences in the patient demographics, injury characteristics, prehospital care, ICU structure and process of care, and/or healthcare costs.

Implications for Clinical Practice and Health Policy

The findings of my thesis have important implications for clinicians. The effectiveness of using invasive ICP monitoring technology in improving patient outcomes has long been questioned, and my research showed a consistent and strong association between ICP monitoring use and lower risk of death among TBI

patients treated in verified trauma centers. In addition, the findings of my research can help clinicians and stakeholders make a more informed choice about the management of refractory intracranial hypertension following TBI. Clinicians may also help patients and their designated decision makers to set realistic expectations for the potential advantages associated with early tracheostomy in TBI patients, which include shorter mechanical ventilation, ICU and hospital stay, but not lower mortality.

For policy makers, the finding of lower TBI mortality with higher hospital-specific rates of ICP monitoring provides quality improvement initiatives with an easily measured performance indicator and an actionable quality benchmark. Furthermore, questions have been raised regarding the futility of decompressive craniectomy and its long-term economic implications for the cost-constrained healthcare system. My research showed that decompressive craniectomy is a more attractive strategy for third-party healthcare payers, relative to barbiturate coma, but the relative economic advantage may be less apparent among older patients. Using value of information methods, I demonstrated that the value of future TBI research might vary based on the type of additional evidence sought. These findings can help policy makers to prioritize TBI research funding. In addition, my research showed that varying the timing of an ICU process of care for severe TBI patients, such as tracheostomy, may have significant implications for resource utilization, including mechanical ventilation days and ICU and hospital length of stay.

These studies demonstrated that health services research offers several advantages over other research methodology. This type of research can be conducted using available resources, is relatively inexpensive, and can provide real-world effectiveness data. In situations where prospective observational studies or randomized trials may not be feasible due to impractical sample sizes or very specific patient subgroups, health services research methods provide an opportunity to answer important questions for both clinicians and policy makers.

Directions for Future Research

The studies in this thesis provide a framework for using the methods of health services research to evaluate the relationship between the ICU process of care and outcome in the TBI population. As demonstrated in this thesis, investigators of the relationship between the process of care and TBI outcome should account for the potential interaction between this relationship and important structural variables to capture the complexity of healthcare delivery.

Future studies of ICP monitoring should elucidate its impact on functional outcome and quality of life for TBI patients. While neuropsychological performance is an important domain to measure in TBI patients, previous studies did not find an independent association between raised ICP and neuropsychological function among survivors.[125] Therefore, neuropsychological tests might not be suitable primary outcome measures for ICP monitoring studies. The optimal ICP threshold

for treatment and the significance of waveform analysis are other important areas to explore in future research.

Considerable uncertainty remains around the decision to choose the optimal treatment for refractory intracranial hypertension among severe TBI patients. Further research, particularly longitudinal studies on the natural history of severe TBI patients, is crucial to make more informed treatment decisions, potentially spare patients unnecessary harm, and decrease costs. The efficacy of other treatment options, such as whole-body and selective brain cooling, should also be tested in the future. I also suggest dedicating more research to establishing definitions for treatment futility among severe TBI patients. Such research should examine the perspectives of patients, families, clinicians, policy makers, and the general public.

Future studies of tracheostomy in the TBI population should focus on identifying more accurate patient selection criteria for tracheostomy. By targeting patients who will require tracheostomy, the benefit of performing the procedure early can be maximized. Instead of focusing on whether early tracheostomy offers a small survival benefit in TBI patients, further studies should address other patient- and family-centered outcomes, such as comfort, communication, and long-term quality of life. Other important areas to explore are the definition of 'too late' tracheostomy and the cost-consequences of varying tracheostomy timing from the perspective of the healthcare payer.

Other ICU processes of care that can be studied in the TBI population using the same methodology include the value of invasive monitoring for global and focal cerebral ischemia, the comparative effectiveness of cerebral ischemia treatment options, optimal mechanical ventilation strategies, safe extubation criteria, blood transfusion threshold, agitation and dysautonomia management, and optimal timing and extent of nutritional support. The general methods of this thesis may also serve as a framework to study the processes of care outside the ICU, such as prehospital resuscitation and transport strategies, and the timing, intensity and patient selection for rehabilitation.

Other relationships between domains of the Donabedian model should be investigated in the TBI population, including the structure-outcome relationship.[103] Potentially relevant structural factors include whether the ICU is specialized in neurotrauma care, the ICU nurse-to-patient ratio, the presence of TBI management protocols, the qualifications of intensivists and other healthcare providers. Further, it is important to test whether these organizational structures moderate the process-outcome relationship. Studies of organizational structure should also expand to include interorganizational relationships in a healthcare system. For example, it is important to examine the effect of interorganizational ties, such as hospital-rehabilitation center-nursing home networks, on the attitude toward TBI prognostication, withdrawal of life support and patient outcomes.

Processes and structural variables may influence health outcome differently at different levels. These factors may also interact with each other. Researchers should

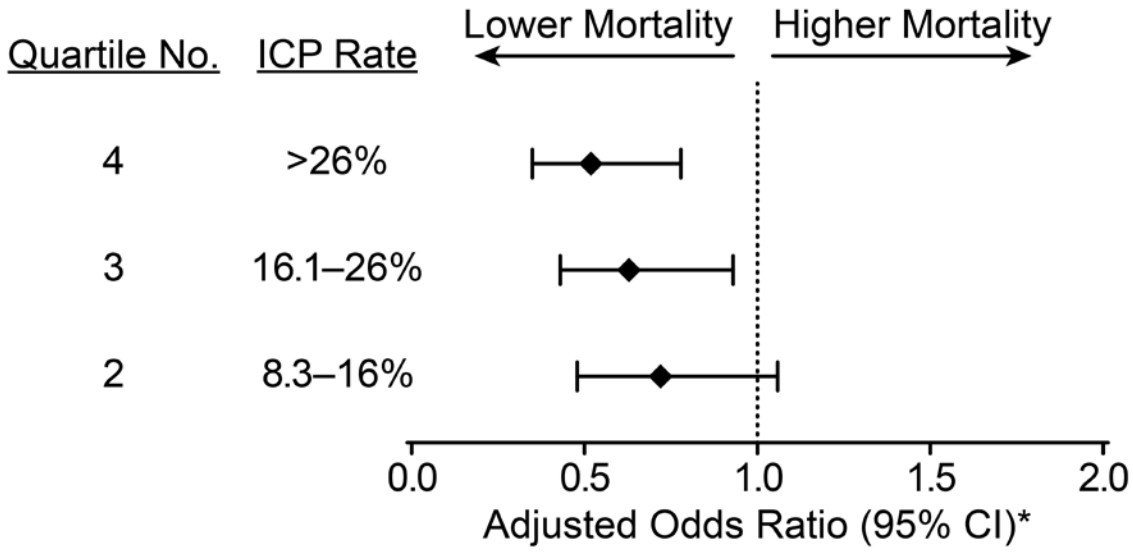
look to multilevel analytical techniques that account for the nested structure of the data at different levels. Multilevel analytic models can help to better understand what determines variations in the structure, process, and outcomes at different levels of a healthcare system. Better understanding of the variations, in turn, may enable us to identify ways to improve the structures and processes of care to achieve better outcomes for TBI patients.

The expansion of data collection on the TBI population by administrative databases may add substantial value to future health services research and quality improvement initiatives. While it might not be feasible for administrative databases to capture long-term outcomes for TBI patients, the use of standardized data collection instruments to record more detailed information on patient and injury characteristics and structures and processes of hospital care can be more practical.

Given the complexity of the healthcare system, researchers should consider a more diverse set of research designs, such as mixed methods. Combining quantitative methods with qualitative research allows researchers to collect more detailed information that may not be attainable through quantitative approaches alone. For example, qualitative research can supplement quantitative studies by exploring the mechanisms of inconsistencies that may exist in the structure-process-outcome relationships at different levels of analysis. Therefore, mixed methods may help to construct a more complete picture of a healthcare system and identify ways to improve its performance.

An important goal of health services research is to provide information and tools that policy makers can use to achieve better quality of care and thereby improve patient outcomes. Keeping this goal in mind has implications for the selection of research topics and study designs. Studies that focus on actionable processes and structural factors should take precedence over research relating to immutable dimensions of healthcare delivery.

Figure 2.1: Forest plot of adjusted odds ratios of death after severe traumatic brain injury at the different hospital quartiles of intracranial pressure monitoring use

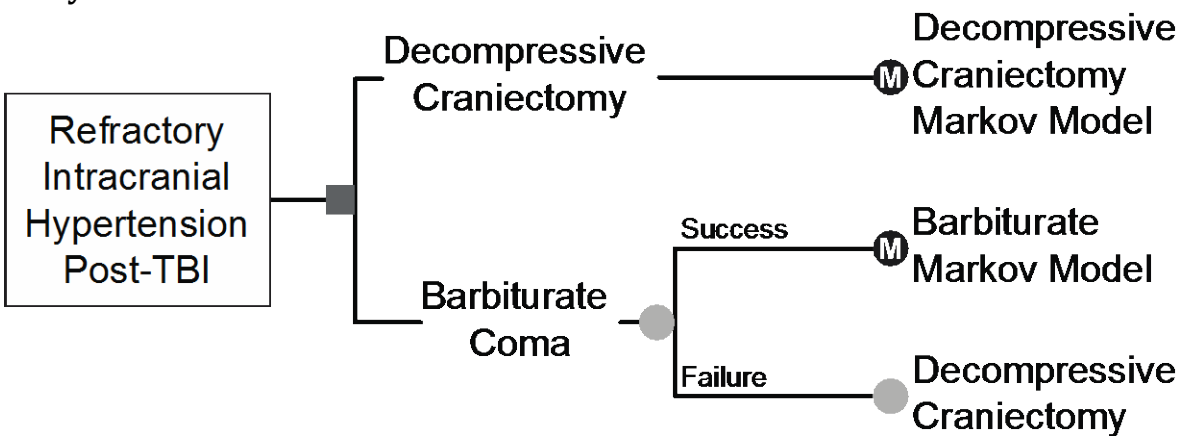


Legend: Quartile 4 has the highest rate of intracranial pressure (ICP) monitoring and Quartile 1 (the reference) has the lowest. The dotted line represents the odds of dying at the reference quartile (Quartile 1).

ICP: intracranial pressure; CI: confidence interval.

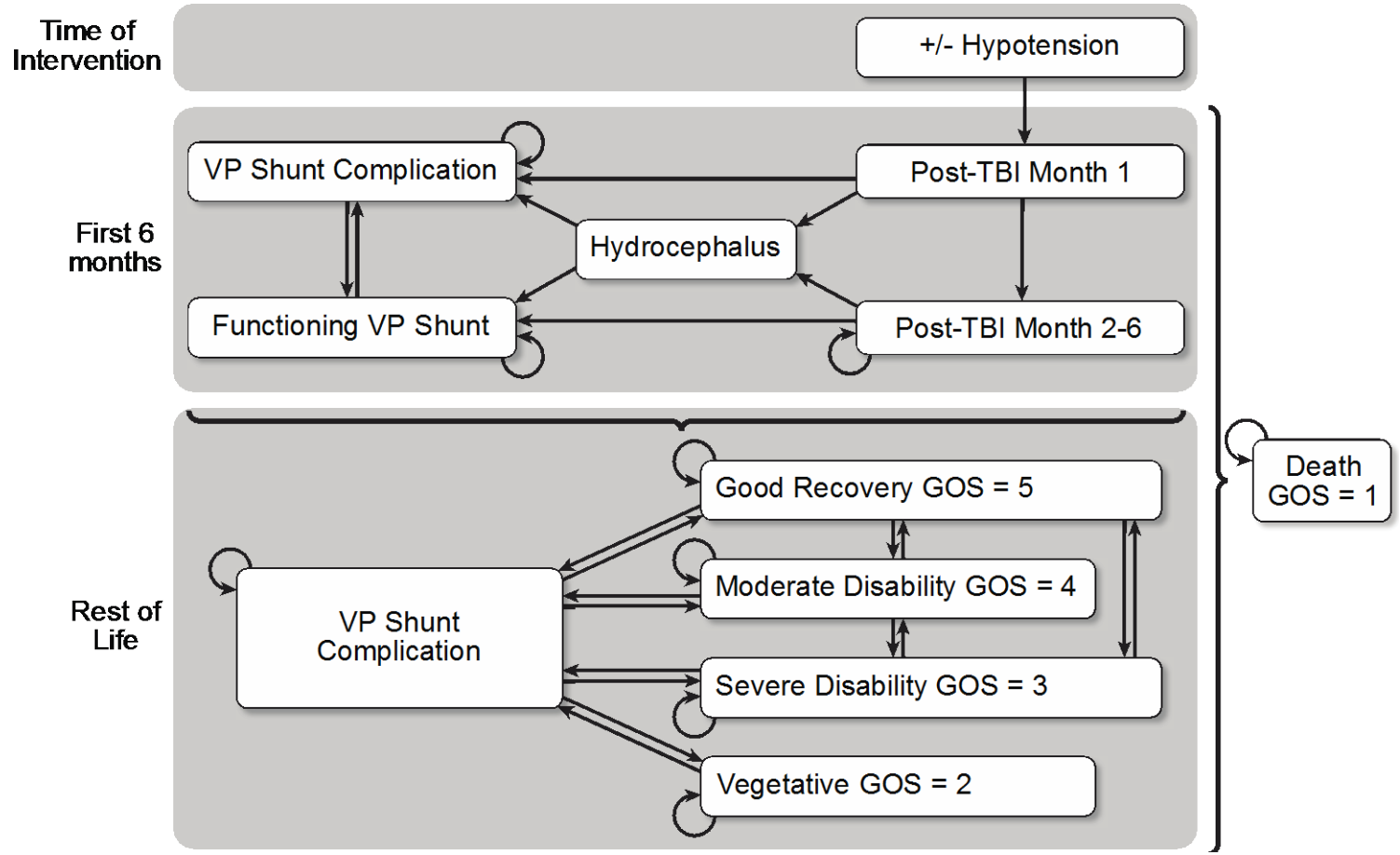
* Odds ratios were estimated using a random-intercept multilevel model with hospital-specific ICP monitoring rate (categorized into quartiles) as the main exposure and in-hospital mortality as the outcome of interest. Patient-level covariates were: age, gender, comorbid illnesses, Glasgow Coma Scale motor score, abbreviated injury scale score for body region head, hypotension on admission, type of intracranial lesion, mechanism of injury, type of insurance. Hospital-level covariates were: volume of traumatic brain injury patients per center, teaching status and number of hospital beds.

Figure 3.1: Schematic representation of the general structure of the decision analytic model



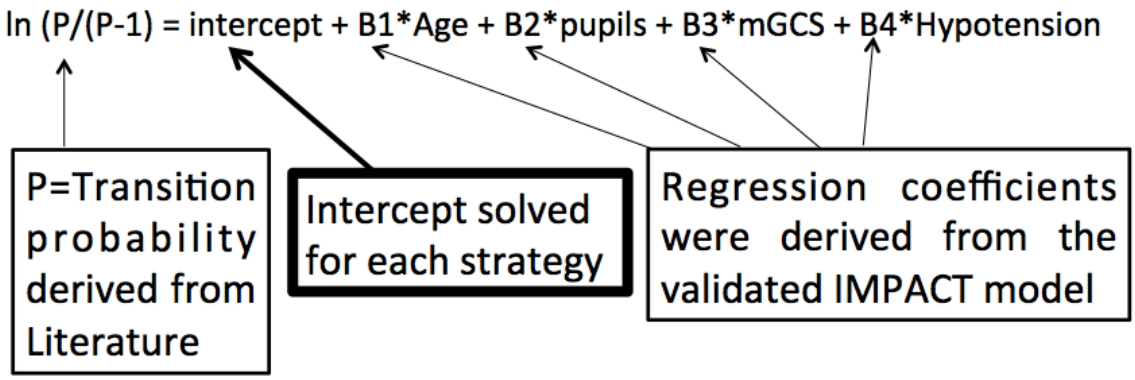
Legend: Schematic representation of the general structure of the decision analytic model highlighting the management strategy for refractory intracranial hypertension following traumatic brain injury (TBI), decompressive craniectomy or barbiturate coma, and the initial chance nodes after the decision point leading to Markov models.

Figure 3.2: Schematic representation of Markov model structure



Legend: Schematic representation of Markov model structure used to model the short-term (first 6 months) and long-term (rest of life until death) outcomes of patients with refractory intracranial hypertension secondary to traumatic brain injury treated with either decompressive craniectomy or barbiturate coma.
GOS: Glasgow Outcome Scale; TBI: traumatic brain injury; VP shunt: ventriculoperitoneal shunt.

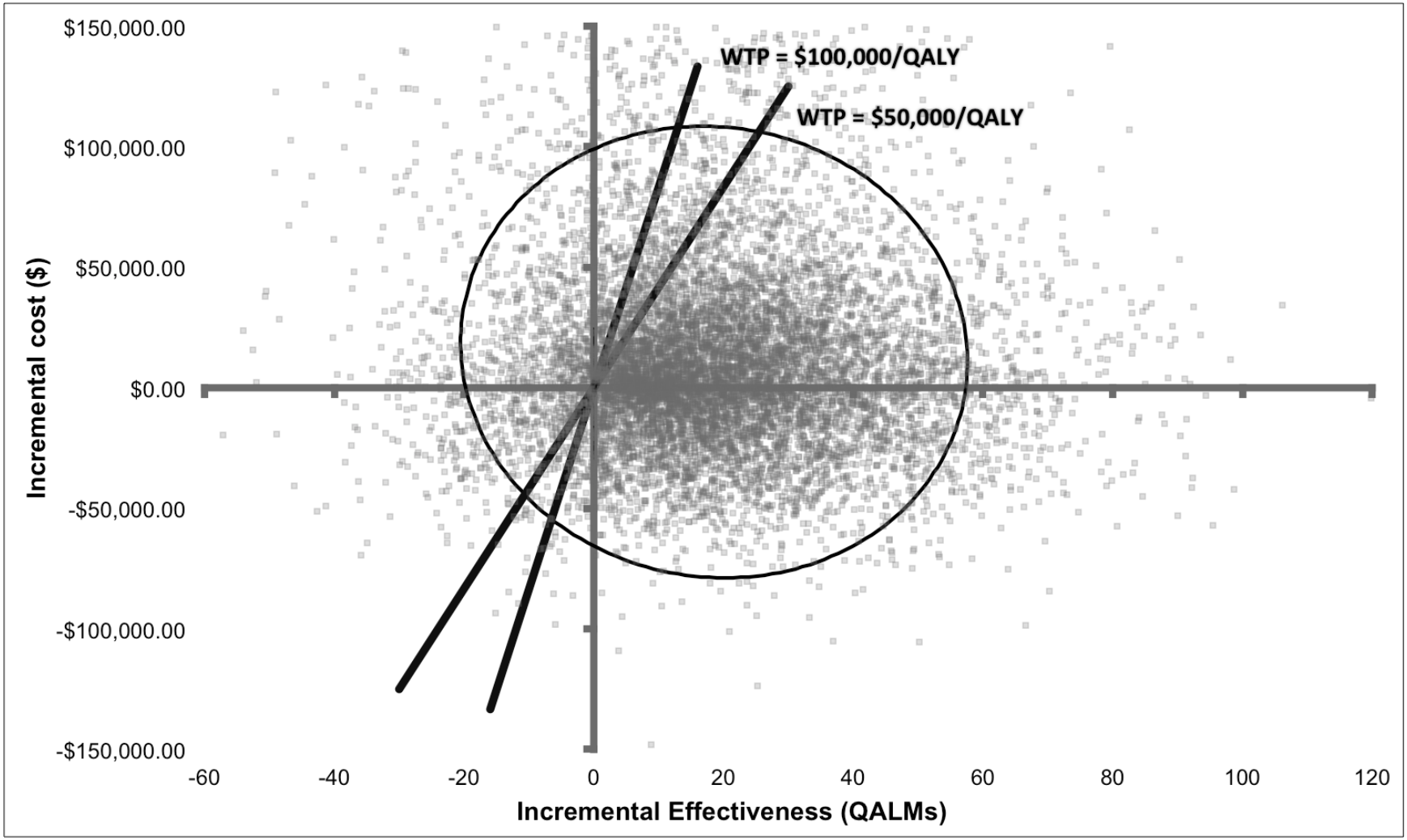
Figure 3.3: The regression model used to calculate individual patients' transition probabilities to one of Glasgow Outcome Scale categories



- B1=0.038
- B2=0 (bilaterally reactive pupils) or 0.6 (one reactive pupil)
- B3=1.36 (mGCS=1) or 1.74 (mGCS=2) or 1.1 (mGCS=3) or 0.53 (mGCS=4) or 0 (mGCS=5)
- B4=0.59

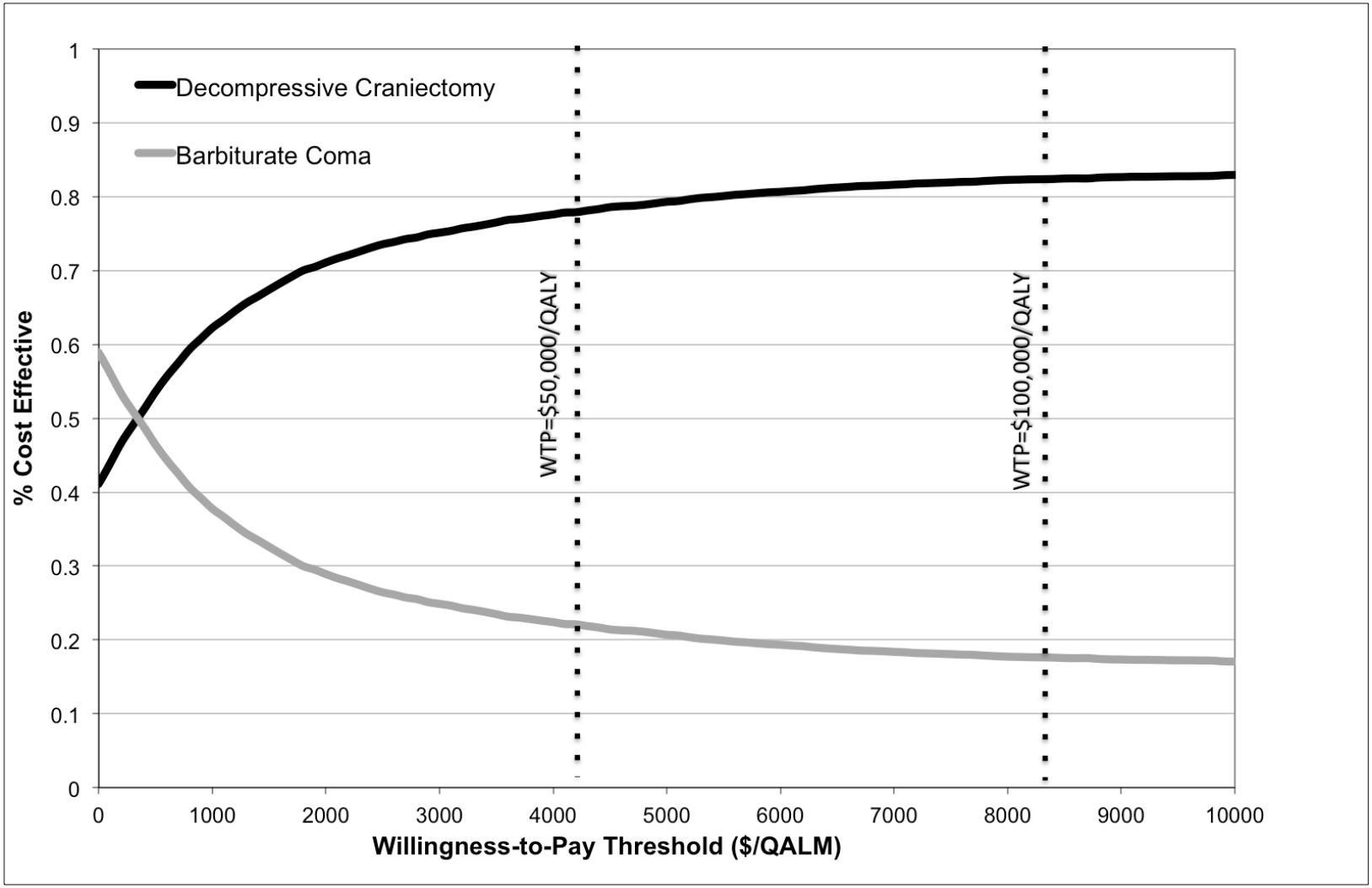
Legend: This model was based on the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model for TBI long-term outcome.[68,192]
IMPACT: International Mission for Prognosis and Analysis of Clinical Trials; mGCS: Glasgow Coma Scale motor score

Figure 3.4: A scatterplot of incremental cost-effectiveness ratios (ICERs) comparing incremental cost and incremental effectiveness of decompressive craniectomy relative to barbiturate coma



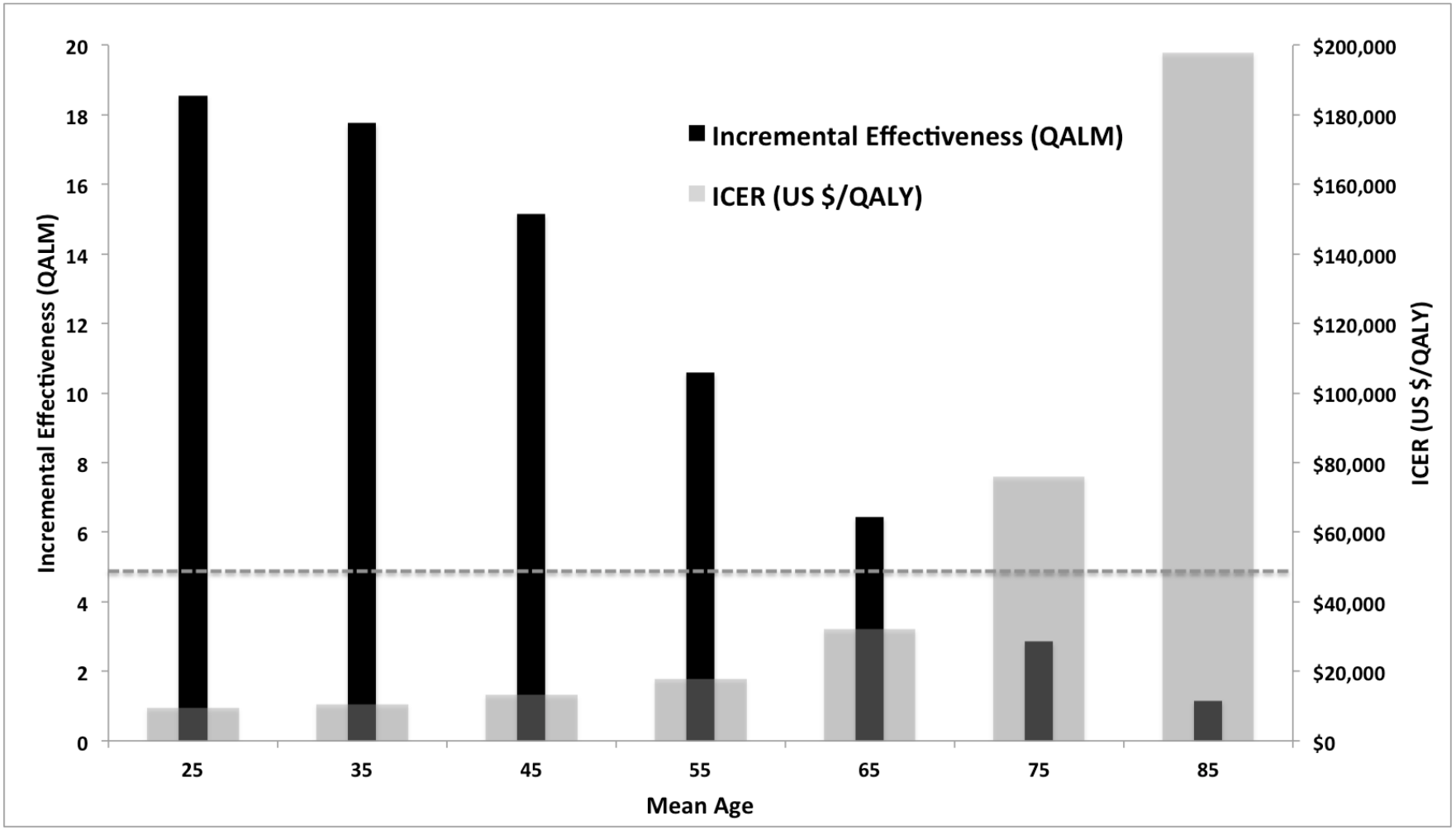
Legend: In this figure, mean ICERs from 10,000 samples are plotted (each sample represents 1,000 microsimulation trials). Decompressive craniectomy results in prolonged quality-adjusted survival (incremental effectiveness>0) 86% of the time, but at an increased cost (incremental cost>0) in the majority of cases. All points to the right of and below a line representing society's willingness-to-pay (WTP) threshold are considered cost effective. At a WTP threshold of $50,000/quality-adjusted life years (QALY), decompressive craniectomy is the most cost effective strategy 78% of the time. At a WTP threshold of $100,000/QALY, decompressive craniectomy is the most cost effective strategy 82% of the time. The ellipse identifies location of 95% of the simulation samples.
QALM: quality-adjusted life months; QALY: quality-adjusted life years; WTP: willingness-to-pay.

Figure 3.5: The cost-effectiveness acceptability curve comparing decompressive craniectomy and barbiturate coma



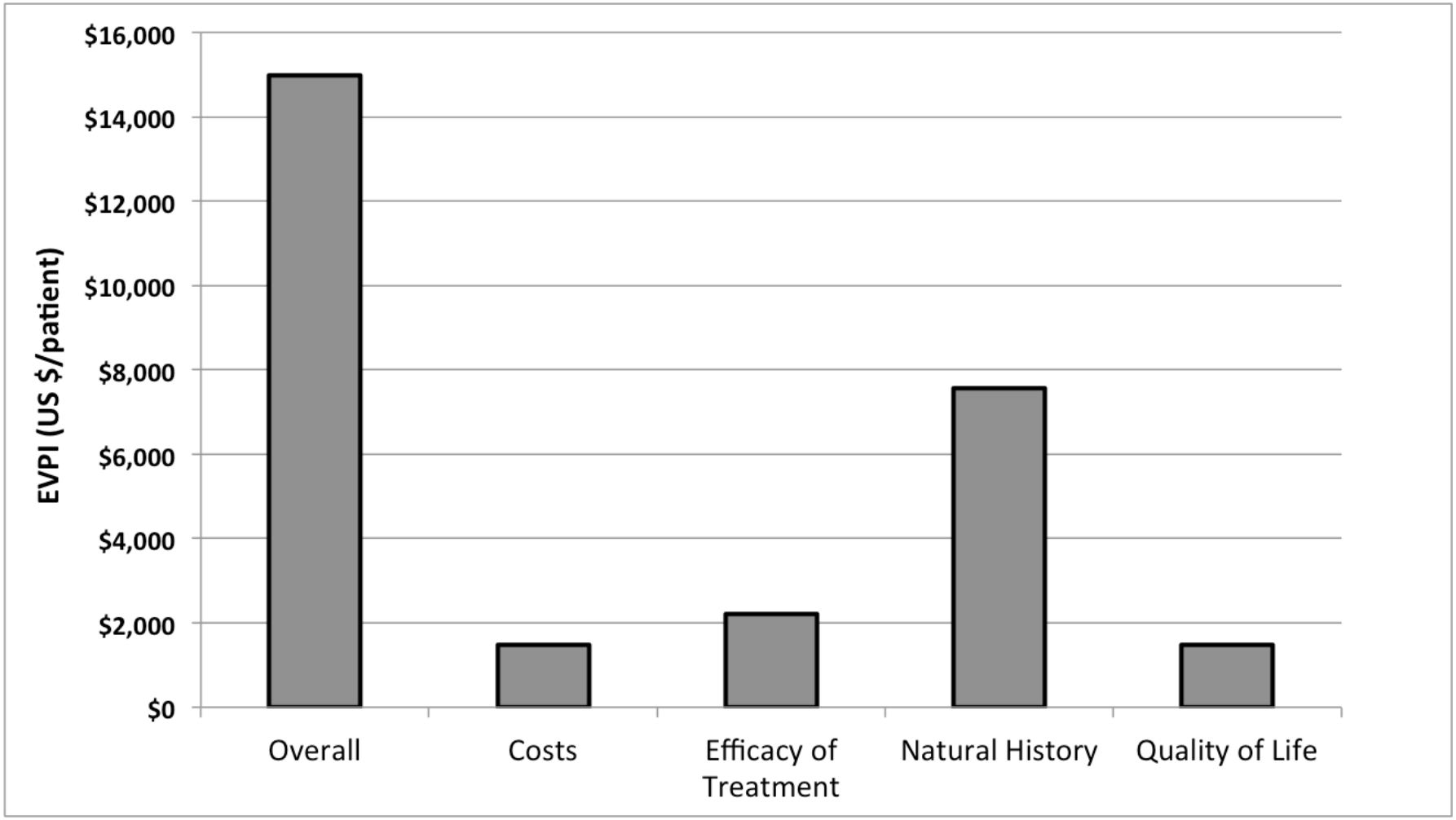
Legend: The cost-effectiveness acceptability curve shows the proportion of time that a particular strategy is the most cost-effective option at a given willingness-to-pay (WTP) threshold. At a WTP threshold of less than $6,000/QALY (i.e. $500/QALM), barbiturate coma is the most cost-effective option. Conversely, if WTP exceed $12,000/QALY, decompressive craniectomy becomes the most cost-effective strategy in the majority of cases.
QALM: quality-adjusted life months; QALY: quality-adjusted life years; WTP: willingness-to-pay

Figure 3.6: The relationship between mean age of simulated patients and incremental cost-effectiveness of decompressive craniectomy relative to barbiturate coma



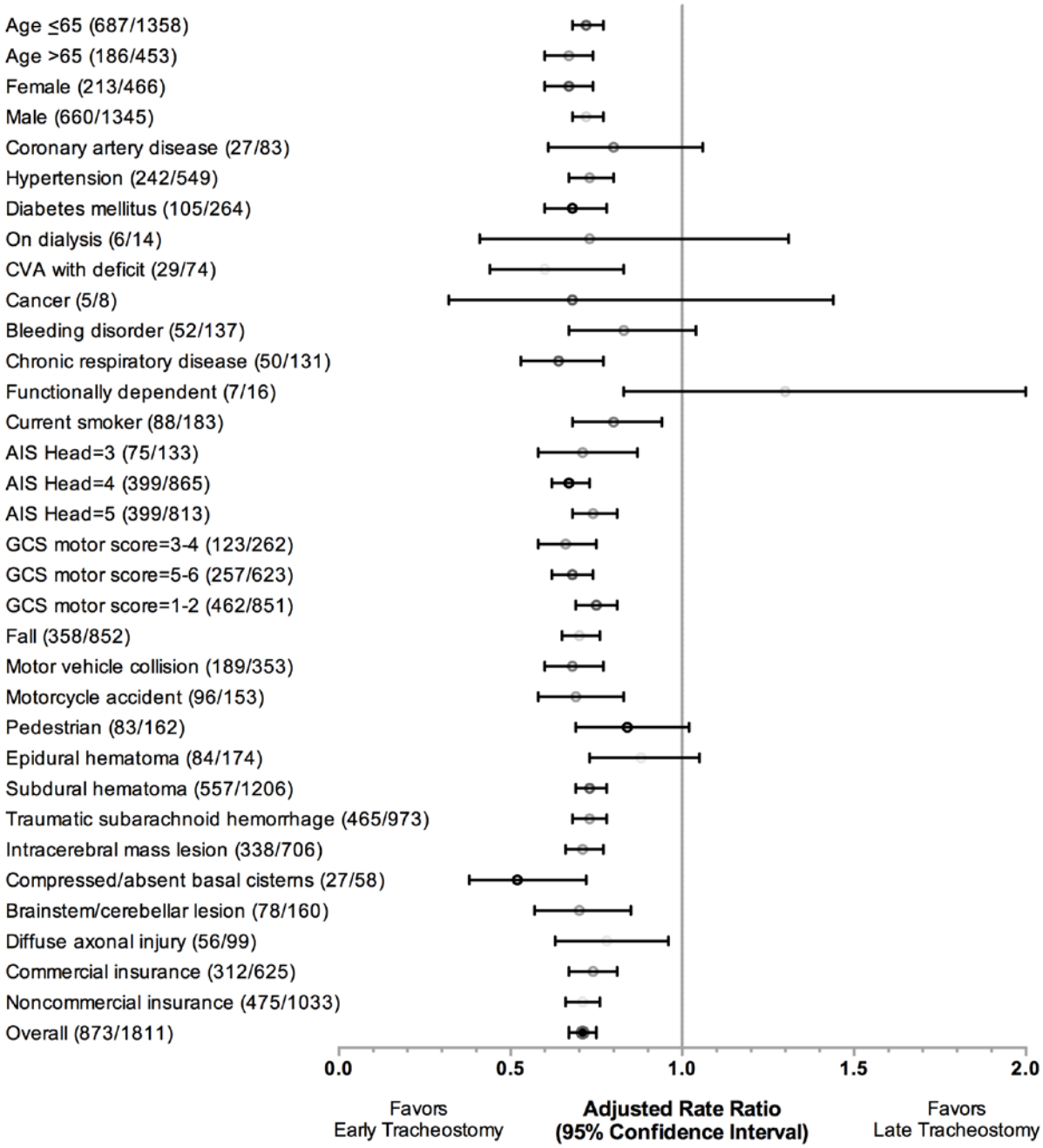
Legend: The relationship between mean age of simulated patients and incremental cost-effectiveness of decompressive craniectomy, relative to barbiturate coma, for refractory intracranial hypertension following traumatic brain injury. The dashed horizontal line represents the commonly cited willingness-to-pay threshold of $50,000/QALY.
ICER: incremental cost-effectiveness ratio; QALM: quality-adjusted life months; QALY: quality-adjusted life years

Figure 3.7: The expected value of perfect information analysis



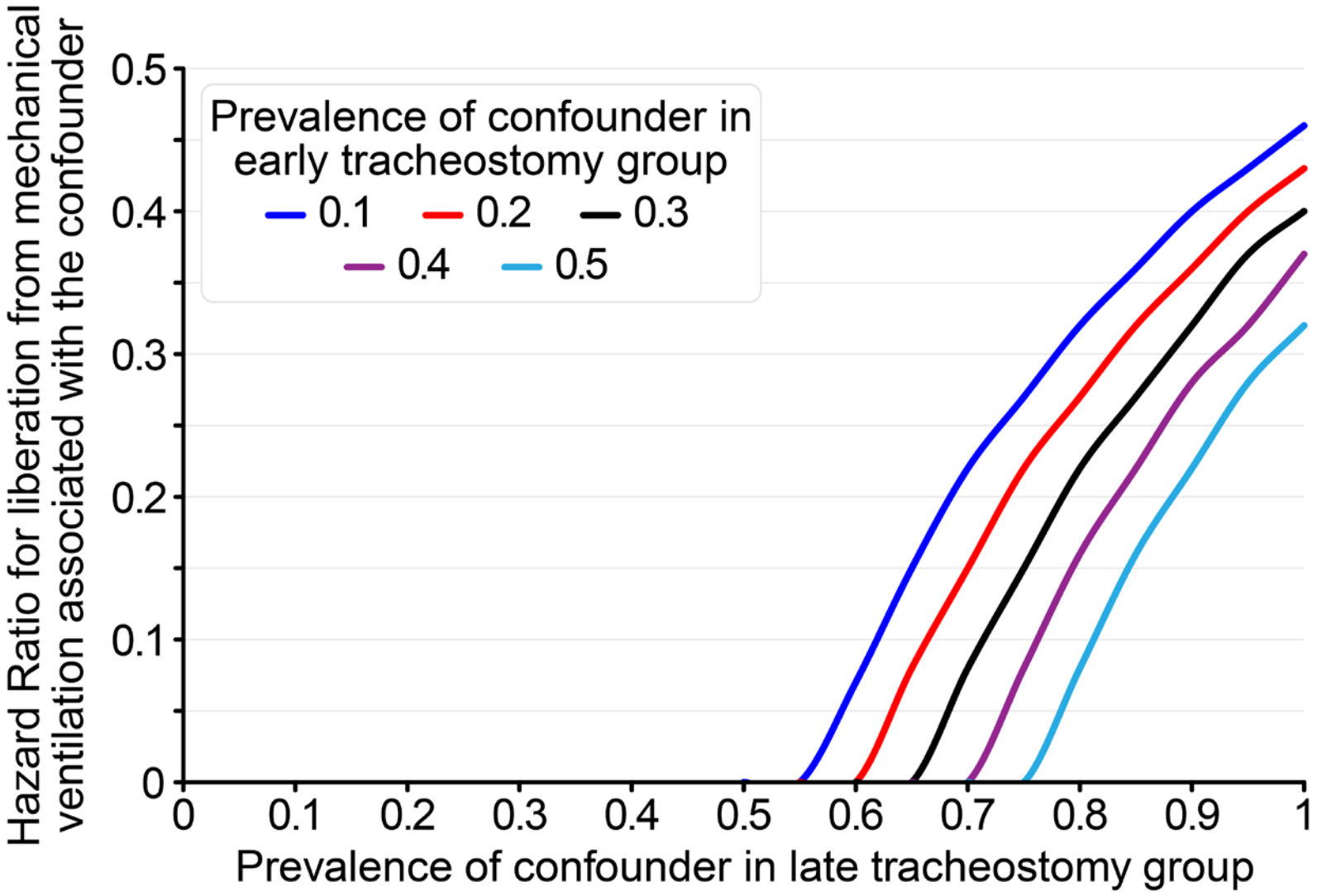
Legend: The expected value of perfect information (EVPI) is the expected monetary benefit per patient of a hypothetical study that would eliminate all parameter uncertainty (or uncertainty in certain parameters of interest in case of partial EVPI). More research is justified if the expected benefit to future patients (estimated as the product of EVPI per patient and the population that is expected to benefit from future research) exceeds the cost of proposed research. The calculated total EVPI was $14,982/patient at a willingness-to-pay of $50,000/QALY. When one considers that 1.37 million Americans sustain traumatic brain injury (TBI) annually and 10% of severe TBI patients (10% of all TBIs) develop refractory intracranial hypertension, perfect information about the variables in the model would be worth more than $205 million over 1 year (assuming information are useful for only 1 year). Therefore, it would be worthwhile to invest in funding future studies to obtain better information about these variables. Partial EVPI calculation showed that further research on the natural history of severe TBI patients with refractory intracranial hypertension would be most valuable.
EVPI: expected value of perfect information

Figure 4.1: Adjusted rate ratios of mechanical ventilation days comparing early versus late tracheostomy among pre-specified subgroups



Legend: Forrest plot of adjusted rate ratio for mechanical ventilation days by subgroup. Rate ratio of mechanical ventilation days for patients who underwent early tracheostomy (≤8 days) compared with those who had late tracheostomy (>8 days). An x-axis value of 1 denotes null effect. Values to the left of 1 indicated fewer mechanical ventilation days with early tracheostomy. CVA: cerebrovascular accident; AIS: Abbreviated Injury Score; CGS: Glasgow Coma Scale.

Figure 4.2: Influence of unmeasured hypothetical confounding factor



Legend: A single unmeasured confounder, or multiple confounding variables acting in concert, could account for the observed advantage of early tracheostomy over late tracheostomy group in terms of likelihood of sooner liberation from mechanical ventilation (i.e. hazard ratio of 2.04 based on the multivariate time-dependent proportional hazards regression) only if the confounder was around 2-10 times more prevalent in the control group AND the confounder decreased the likelihood (i.e. hazards) of liberation from mechanical ventilation by around 93-54%. For example, if the prevalence of the unmeasured confounder was 10% in the early tracheostomy group (exposure) and 60% in the late tracheostomy group (control), and if this confounder decreased the likelihood (hazard) of liberation from mechanical ventilation by 93% (hazard ratio=0.07), then the confounder alone could explain the observed difference in likelihood of liberation from mechanical ventilation between the exposure and control groups.

Table 1.1: Glasgow Coma Scale[24]

Domain	Response	Score
Eye Opening	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best Verbal Response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best Motor Response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion	3
	Abnormal extension	2
	No response	1
Total Score	Based on best responses	3-15 out of 15

Table 1.2: Marshall classification system of traumatic brain injury based on computerized tomography[26]

Class	Definition
Diffuse Injury I	No visible pathology
Diffuse Injury II	Cisterns present, midline shift=0-5 mm, and/or lesion densities present. No mass lesion >25 cc
Diffuse Injury III (swelling)	Cisterns compressed/absent, midline shift=0-5 mm, and/or lesion densities present. No mass lesion >25 cc
Diffuse Injury IV (shift)	Midline shift>5 mm. No mass lesion >25 cc
Evacuated Mass Lesion	Any surgically evacuated lesion
Non-evacuated Mass Lesion	Mass lesion >25 cc not surgically evacuated

mm: millimeters; mass lesion: mixed or high density lesion; cc: cubic centimeters.

Table 1.3: Body Regions and Severity Scoring in the Abbreviated Injury Scale (AIS)[29]

Body Regions:	**Severity Scores:**
External (skin)	0: no injury
Head (including brain)	1: minor (e.g. minor scalp laceration)
Neck	2: moderate (e.g. closed linear skull fracture)
Thorax	3: serious (e.g. cerebral contusion ≤30 cc)
Abdomen/pelvis	4: severe (e.g. cerebral contusion 30-50 cc)
Spine	5: critical (e.g. cerebral contusion >50 cc)
Extremities	6: unsurvivable (e.g. crush injury of the brain stem)

cc: cubic centimeters

Table 1.4: Intracranial lesions and Abbreviated Injury Scale (AIS) predot codes[29]

Intracranial Lesion	AIS* codes
Epidural hematoma	140630, 140632, 140634, 140636
Subdural hematoma	140650, 140652, 140654, 140656
Traumatic subarachnoid hemorrhage	140684
Intracerebral mass lesion	140608, 140610, 140616, 140618, 140624, 140626, 140648
Compressed/absent basal cisterns	140664, 140666, 140672, 140674
Brainstem/cerebellar lesion	140204, 140206, 140208, 140210, 140212, 140214, 140218, 14218, 140299, 140402, 140403, 140404, 140405, 140406, 140410, 140414, 140418, 140422, 140426, 140430, 140434, 140438, 140442, 140446, 1404450, 140458, 140462, 140466, 140470, 140474, 140499
Diffuse axonal injury	140206, 140628

*AIS: abbreviated injury scale.

Table 1.5: Summary of previous studies of the relationship between intracranial pressure monitoring utilization and traumatic brain injury outcome

Study	Design	Sample Size	Eligibility	Exposure/Intervention	Control	Findings
Lane et al. 2000[119]	Retrospective cohort study (14 centers in Ontario, Canada)	541 exposure 4,946 control	Adult TBI patients with AIS head score >3	ICP monitoring	No ICP monitoring	Lower hospital mortality with ICP monitoring (OR=0.77; p=0.02) in an adjusted analysis (adjusted for AIS head, ISS, and injury mechanism)
Bulger et al. 2002[118]	Retrospective cohort study (33 centers in the US)	74 exposure 106 control	Adults with severe blunt TBI and abnormal CT head	Management at aggressive centers (defined as those placing ICP monitors in >50% of patients as indicated by BTF guidelines)	Management at nonaggressive centers (defined as those placing ICP monitors in <50% of patients as indicated by BTF guidelines)	Lower hospital mortality with ICP monitoring (HR=0.43; 95% CI: 0.27-0.66) and no difference in functional outcome in an adjusted analysis (adjusted for age, AIS head, and ISS)
Cremer et al. 2005[151]	Retrospective cohort study (2 centers in the Netherlands)	122 exposure 211 control	Adult TBI patients who remained comatose for >24 hours.	ICP/CPP-guided treatment. ICP was maintained <20 mm Hg, and CPP was maintained >70 mm Hg	MAP was maintained at 90 mm Hg, No ICP monitoring	No significant difference in hospital mortality (34% vs. 33%, p=0.87) or functional

						outcome at ≥12 months
Mauritz et al. 2008[154]	Retrospective cohort study (32 centers in Austria)	825 exposure 1,031 control	Adults with severe TBI who survived in ICU for >3 days.	ICP monitoring	No ICP monitoring	No significant difference in hospital mortality (39% vs. 38%).
Shafi et al. 2008[161]	Retrospective cohort study (Level I & II trauma centers participating in NTDB, US)	708 exposure 938 control	Adults with blunt TBI, aged 20-50 years, who survived in ICU for >2 days.	ICP monitoring	No ICP monitoring	Higher hospital mortality with ICP monitoring (OR=1.8; p<0.0001) and worse functional outcome at discharge in adjusted analyses (adjusted for ISS, revised trauma score, head AIS, motor GCS score, craniotomy, spinal injury, cardiac disease, and in-hospital complications)
Biersteker et al. 2012[150]	Prospective cohort study (5 centers in the Netherlands)	123 exposure 142 control	Adults with severe blunt TBI who met indications for ICP monitoring as per BTF guidelines	Invasive ICP monitoring	No ICP monitoring	No significant difference in mortality (OR 0.93; p=0.83) or functional outcome at 6 months in adjusted analyses (adjusted for age,

						GCS, pupils, basal cisterns status, lesion volume)
Chesnut et al. 2012[124]	Randomized controlled trial (6 hospitals in Ecuador and Bolivia)	157 intervention 167 control	Adults with severe TBI admitted to ICU	Invasive ICP monitoring-based protocol	Serial imaging and clinical examination-based protocol	No significant difference in the primary outcome (56 vs. 53; p=0.49); which was a composite measure based on percentile performance across 21 measures of functional and cognitive status. No significant difference in mortality at 6 months (39% vs. 41%; p=0.60)
Farahvar et al. 2012[120]	Retrospective cohort study (22 centers in the state of New York)	1202 exposure 244 control	Adults with severe TBI who received ICP lowering therapy	ICP monitoring	No ICP monitoring	Lower mortality with ICP monitoring (OR=0.64; p=0.05) at 2 weeks in an adjusted analysis (adjusted for age, hypotension, pupils, GCS score, CT findings)

AIS: Abbreviated Injury Scale; BTF: Brain Trauma Foundation Guidelines; GCS: Glasgow Coma Scale; HR: hazard ratio; ICP: intracranial pressure; ICU: intensive care unit; ISS: injury severity score; NTDB: National Trauma Data Bank; OR: odds ratio; TBI: traumatic brain injury; US: United States.

Table 1.6: Summary of randomized trials of decompressive craniectomy or barbiturate coma for refractory intracranial hypertension following traumatic brain injury

Study	Design	Sample Size	Eligibility	Intervention	Control	Findings
Eisenberg et 1988[132]	Randomized controlled trials (5 centers in the US)	37 Intervention 36 Control	Adults with severe TBI, aged 15-50 years, who developed intracranial hypertension refractory to first-line medical treatment and after evacuation of surgical lesions	High-dose phenobarbital infusion in addition to medical therapeutic options	Continuation of medical therapy without barbiturate administration. Cross-over to barbiturate was allowed if conventional treatment fails according to prespecified criteria (cross-over rate was 72%)	Barbiturate therapy was more effective at controlling high ICP in an adjusted analysis (p=0.02), but the effect was not statistically significant in a crude analysis (p=0.12). Barbiturate responders had higher likelihood of survival at 1 month compared to non-responders (89% vs. 14%).
Jiang et al. 2005[250]	Randomized controlled trials (5 centers in China)	245 Intervention 241 Control	Adults with severe TBI and unilateral swelling or contusion, aged 15-70 years, who developed intracranial	Unilateral frontotemporoparietal decompressive craniectomy (12 X 15 cm) and medical treatment	Limited unilateral temporoparietal craniectomy (6 x 8 cm) and medical treatment	The standard (larger) craniectomy group were more likely to have a favorable outcome on the Glasgow Outcome Scale at 6 months

			hypertension refractory to first-line medical treatment and after evacuation of surgical lesions			(40% vs. 29%; p=0.01) and lower mortality (26% vs. 35%; p=0.03)
Perez et al. 2008[186]	Randomized controlled trial (single center in Spain)	22 Intervention 22 Control	Adults with severe TBI, aged 15-76 years, who developed intracranial hypertension refractory to first-line medical treatment and after evacuation of surgical lesions	High-dose phenobarbital	High-dose thiopental	Thiopental was more effective at controlling ICP (p=0.03). Unfavorable outcome at 6 months on the Glasgow Outcome Scale were similar (p=0.17)
Cooper et al. 2011[129]	Randomized controlled trial (15 centers in Australia, New Zealand, and Saudi Arabia)	73 exposure 82 control	Adults with diffuse severe TBI and no surgical lesions, aged 15-59 years, who developed intracranial hypertension refractory to first-line medical treatment	Bilateral frontotemporoparietal decompressive craniectomy and medical treatment	Medical treatment alone (e.g. barbiturate therapy and/or mild hypothermia)	Decompressive craniectomy group had worse scores on Extended Glasgow Outcome Scale (OR=1.84; p=0.03) with similar mortality risk (19% vs. 18%). After adjusted analysis, there was no significant difference in

						functional outcome between the two groups.

ICP: intracranial hypertension; OR: odds ratio; TBI: traumatic brain injury.

Table 1.7: Summary of previous studies of tracheostomy timing among traumatic brain injury patients

Study	Design	Sample Size	Eligibility	Exposure/Intervention	Control	Findings
Sugerman et al. 1997	A subgroup of a randomized controlled trial (5 centers in the US)	35 intervention 32 control	Adults with severe TBI who were intubated for >3 days	Early tracheostomy; performed between 3-5 days of admission	Continued intubation or tracheostomy between 10-14 days after admission	No significant difference in ICU stay (mean=16 vs. 19 days), pneumonia (49% vs. 53%; p=0.71), or mortality (14% vs. 3%; p=0.11)
Bouderka et al. 2004	Randomized controlled trials (single center in Morocco)	31 intervention 31 control	Adults with severe TBI and had cerebral contusions	Tracheostomy on day 5 or 6 post-admission	Prolonged intubation	Mechanical ventilation was shorter in the tracheostomy group (mean ventilation days=14.5 vs. 17.5; p=0.02). No significant difference in mortality (39% vs. 23%; p=0.72), pneumonia (58% vs. 61%; p=0.79), or ICU length of stay (numbers were not reported)

Ahmed et al. 2007	Retrospective cohort study (single center in Neptune, New Jersey)	27 exposure 28 control	Adults with severe TBI who survived for >3 days and underwent tracheostomy	Early tracheostomy; defined as within 7 days of admission	Late tracheostomy; performed after 7 days of admission	Early tracheostomy was associated with shorter ICU stay (mean=19 vs. 25.8 days; p=0.008). No significant difference in ventilation days (mean=15.7 vs. 20 days; p=0.57), hospital stay (mean=24 vs. 28 days; p=0.42), pneumonia (41% vs. 50%; p=0.59), or hospital mortality (numbers were not reported).
Rizk et al. 2011	Retrospective cohort study (26 centers in in the states of Pennsylvania)	1577 exposure 1527 control	Adults with severe TBI and at least one associated injury to other body system, who underwent tracheostomy	Early tracheostomy; defined as within 7 days of admission	Late tracheostomy; performed after 7 days of admission	In adjusted analyses, early tracheostomy was associated with shorter ICU and hospital stay (OR=0.23 and 0.34, respectively, p<0.0001), less pulmonary complications

						(OR=0.48; p<0.0001), but higher in-hospital mortality (OR=2.12; p<0.0001). Analyses adjusted for age, sex, race, preexisting conditions, associated injuries, ISS, and injury type
Wang et al. 2011	Retrospective cohort study (single center in Taiwan)	16 exposure 50 control	Adults with severe TBI who underwent tracheostomy	Early tracheostomy; defined as within 10 days of admission	Late tracheostomy; performed after 10 days of admission	Early tracheostomy was associated with shorter mechanical ventilation (mean=13.7 vs. 23.4 days; p value was reported as significant), shorter ICU stay (mean=14.9 vs. 22.1 days; p<0.001), and lower incidence of pneumonia (44% vs. 76%; p=0.04). No significant

						difference in 1-year mortality (12% vs. 8%; p=0.63), or hospital length of stay (mean=38 vs. 46.8 days; p=0.62)

ICU: intensive care unit; ISS: injury severity score; OR: odds ratio; TBI: traumatic brain injury

Table 2.1: Baseline characteristics of patients who were managed with and without intracranial pressure monitoring

Characteristic	ICP group (N=1,874)	No ICP group (N=8,754)	Standardized difference
Patient-level characteristics			
Age-median (IQR)	43 (26-56)	53 (31-72)	0.45
Gender-no. (%)			
Female	420 (22.4)	2611 (29.8)	0.17
Race-no. (%)			
Black	183 (9.8)	958 (10.9)	
White	1334 (71.2)	6316 (72.2)	0.07
Other Race	247 (13.2)	1084 (12.4)	
Unknown/missing	110 (5.9)	396 (4.5)	
Comorbid illnesses-no. (%)			
Coronary artery disease	49 (2.6)	447 (5.2)	0.13
Hypertension	379 (20.4)	2360 (27.3)	0.16
Diabetes	159 (8.6)	976 (11.3)	0.09
On dialysis	15 (0.8)	87 (1.0)	0.02
CVA with residual deficit	49 (2.6)	335 (3.9)	0.06
Cancer	3 (0.2)	121 (1.4)	0.14
Bleeding disorder	73 (3.9)	717 (8.3)	0.18
Chronic respiratory disease	74 (4.0)	485 (5.6)	0.07
Functionally dependent	11 (0.6)	103 (1.2)	0.07
AIS head-no. (%)			
3	109 (5.8)	1111 (12.7)	0.31

4	676 (36.1)	3678 (42.0)	
5	1089 (58.1)	3965 (45.3)	
Intracranial lesion-no. (%)			
Epidural hematoma	242 (12.9)	767 (8.8)	0.13
Subdural hematoma	1274 (68.0)	5401 (61.7)	0.13
Traumatic subarachnoid hemorrhage	1038 (55.4)	4104 (46.9)	0.17
Intracerebral mass lesion	167 (8.9)	417 (4.8)	0.16
Compressed/absent basal cisterns	102 (5.4)	238 (2.7)	0.14
Brainstem/cerebellar lesion	213 (11.4)	835 (9.5)	0.06
Hypotension (SBP <90)-no. (%)	52 (2.8)	532 (6.1)	0.16
Missing SBP values-no. (%)	4 (0.2)	52 (0.6)	
Motor GCS score-median (IQR)	1 (1-3)	1 (1-3)	0.01
Total GCS score-median (IQR)	3 (3-5)	3 (3-6)	0.02
Mechanism-no. (%)			
Fall	765 (40.8)	4800 (54.8)	0.29
Motor vehicle collision	398 (21.2)	1442 (16.5)	
Motorcycle	166 (8.9)	500 (5.7)	
Pedestrian	209 (11.2)	636 (7.3)	
Other	336 (17.9)	1376 (15.7)	
Type of insurance-no. (%)			
Commercial	721 (38.5)	2590 (29.6)	0.25
Non-commercial	1072 (57.2)	5343 (61)	

Unknown	81 (4.3)	821 (9.4)	
Hospital-level characteristics			
Hospital type			
Non-profit	1770 (94.5)	8331 (95.2)	0.03
For profit	104 (5.6)	423 (4.8)	
No. of beds			
≤200	62 (3.3)	171 (2.0)	
201-400	350 (18.7)	1577 (18.0)	0.11
401-600	557 (29.7)	2388 (27.3)	
>600	905 (48.3)	4618 (52.8)	
Teaching status			
University	1155 (61.6)	5288 (60.4)	0.15
Community	657 (35.1)	2906 (33.2)	
Non-teaching	62 (3.3)	560 (6.4)	
Trauma center level			
Level I	1449 (77.3)	6885 (78.7)	0.03
Level II	425 (22.7)	1869 (21.4)	
Volume of TBI patients			
Quartile 1 (<24 patients)	114 (20.1)	453 (79.9)	
Quartile 2 (25-57 patients)	335 (20.5)	1299 (79.5)	0.06
Quartile 3 (58-95 patients)	477 (16.5)	2412 (83.5)	
Quartile 4 (>96 patients)	948 (17.0)	4590 (82.9)	

ICP: intracranial pressure; IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; TBI: traumatic brain injury.

Table 2.2: Baseline characteristics of patients within strata based on hospital-specific rate of intracranial pressure monitoring utilization

Characteristic	Quartile 1 (N=2,555)	Quartile 2 (N=2,460)	Quartile 3 (N=3,216)	Quartile 4 (N=2,397)
ICP monitoring –no. (%)	102 (4.0)	296 (12.0)	687 (21.4)	789 (32.9)
Patient Characteristics				
Age-median (IQR)	51 (31-69)	51 (30-70)	51 (30-70)	50 (29-69)
Gender-no. (%)				
Female	690 (27.0)	715 (29.1)	951 (29.6)	675 (28.2)
Race-no. (%)				
Black	327 (12.4)	265 (10.8)	317 (9.9)	242 (10.1)
White	1712 (67.0)	1873 (76.1)	2438 (75.8)	1627 (67.9)
Other	424 (16.6)	250 (10.1)	364 (11.3)	293 (12.2)
Unknown/missing	102 (4.0)	72 (2.9)	97 (3.0)	235 (9.8)
Comorbid illnesses-no. (%)				
Coronary artery disease	91 (3.6)	119 (4.9)	173 (5.4)	113 (4.8)
Hypertension	544 (21.7)	604 (24.9)	901 (28.2)	690 (29.1)
Diabetes	250 (10.0)	242 (10.0)	359 (11.3)	284 (12.0)
On dialysis	14 (0.6)	28 (1.2)	32 (1.0)	28 (1.2)
CVA with residual deficit	47 (1.9)	85 (3.5)	158 (5.0)	94 (4.0)
Cancer	43 (1.7)	22 (0.9)	36 (1.1)	23 (1.0)
Bleeding disorder	136 (5.4)	216 (8.9)	278 (8.7)	160 (6.7)
Respiratory disease	120 (4.8)	130 (5.4)	178 (5.6)	131 (5.5)
Functionally dependent	20 (0.8)	24 (1.0)	46 (1.4)	24 (1.0)
AIS head-no. (%)				

3	318 (12.5)	342 (13.9)	353 (11.0)	207 (8.6)
4	1051 (41.1)	975 (39.6)	1357 (42.2)	971 (40.5)
5	1186 (46.4)	1143 (46.5)	1506 (46.8)	1219 (50.9)
Intracranial lesion-no. (%)				
Epidural hematoma	265 (10.4)	219 (8.9)	282 (8.8)	243 (10.1)
Subdural hematoma	1559 (61.0)	1511 (61.4)	2078 (64.6)	1527 (63.7)
Traumatic subarachnoid hemorrhage	1286 (50.3)	1254 (51.0)	1498 (46.6)	1104 (46.1)
Intracerebral mass lesion	106 (4.2)	146 (5.9)	165 (5.1)	167 (7.0)
Compressed/absent basal cisterns	88 (3.4)	84 (3.4)	104 (3.2)	64 (2.7)
Brainstem/cerebellar lesion	314 (12.3)	253 (10.3)	242 (7.5)	239 (10.0)
Hypotension (SBP <90)-no. (%)	18 (0.7)	14 (0.6)	12 (0.4)	12 (0.5)
Missing SBP values-no. (%)	132 (5.2)	158 (6.4)	176 (5.5)	118 (4.9)
Motor GCS score-median (IQR)	1 (1-3)	1 (1-2)	1 (1-2)	1 (1-3)
Total GCS score-median (IQR)	3 (3-6)	3 (3-5)	3 (3-5)	3 (3-6)
Mechanism-no. (%)				
Fall	1312 (51.4)	1269 (51.6)	1735 (54.0)	1249 (52.1)
Motor vehicle collision	390 (15.3)	432 (17.6)	616 (19.2)	402 (16.8)
Motorcycle	163 (6.4)	175 (7.1)	194 (6.0)	134 (5.6)
Pedestrian	198 (7.8)	199 (8.1)	234 (7.3)	214 (8.9)
Other	492 (19.3)	385 (15.7)	437 (13.6)	398 (16.6)
Type of insurance-no. (%)				
Commercial	680 (26.6)	857 (34.8)	1101 (34.2)	673 (28.1)
Non-commercial	1395 (54.6)	1456 (59.2)	1955 (60.8)	1609 (67.1)

Unknown/missing	480 (18.8)	147 (6.0)	160 (5.0)	115 (4.8)
Hospital type-no. (%)				
Non-profit	2512 (98.3)	2208 (89.8)	3082 (95.8)	2299 (95.9)
For profit	43 (1.7)	252 (10.2)	134 (4.2)	98 (4.1)
No. of beds-no. (%)				
≤200	50 (2.0)	7 (0.3)	15 (0.5)	161 (6.7)
201-400	482 (18.9)	483 (19.6)	576 (17.9)	386 (16.1)
401-600	601 (23.5)	689 (28.0)	963 (29.9)	692 (28.9)
>600	1422 (55.7)	1281 (52.1)	1662 (51.7)	1158 (48.3)
Teaching status-no. (%)				
University	1696 (66.4)	1117 (45.4)	2027 (63.0)	1603 (66.9)
Community	579 (22.7)	1068 (43.4)	1122 (34.9)	794 (33.1)
Non-teaching	280 (11.0)	275 (11.2)	67 (2.1)	0 (0.0)
Trauma center level-no. (%)				
Level I	2088 (81.7)	1632 (66.3)	2792 (86.8)	1822 (76.0)
Level II	467 (18.3)	828 (33.7)	424 (13.2)	575 (24.0)
Volume of TBI patients				
Quartile 1 (<24 patients)	95 (3.7)	179 (7.3)	84 (2.6)	209 (8.7)
Quartile 2 (25-57 patients)	397 (15.5)	292 (11.9)	438 (13.6)	507 (21.2)
Quartile 3 (58-95 patients)	720 (28.2)	878 (35.7)	744 (23.1)	547 (22.8)
Quartile 4 (>96 patients)	1343 (52.6)	1111 (45.2)	1950 (60.6)	1134 (47.3)

Strata range from the lowest rate of intracranial pressure (ICP) monitoring (quartile 1) to the highest (quartile 4).
ICP: intracranial pressure; IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; TBI: traumatic brain injury.

Table 2.3: Relationship between intracranial pressure monitoring and in-hospital mortality (patient-level analysis)

Covariate	Odds Ratio	95 % CI	p value
Patient-level characteristics			
ICP monitoring (Yes)	**0.44**	**0.31-0.63**	**<0.0001**
Age (years)			
16 to 24	Reference	NA	
25 to 40	1.20	0.96-1.50	
41 to 54	2.03	1.63-2.52	<0.0001
55 to 64	3.22	2.52-4.11	
65 to 74	3.75	2.83-5.00	
≥75	6.53	4.82-8.84	
Gender (female)	1.04	0.93-1.17	0.51
Comorbid illnesses			
Coronary artery disease	1.35	1.06-1.71	0.01
Hypertension	0.76	0.66-0.87	<0.0001
Diabetes	1.14	0.96-1.34	0.12
On dialysis	2.50	1.51-4.16	0.0007
CVA with residual deficit	0.95	0.73-1.23	0.69
Cancer	2.41	1.54-3.78	0.0002
Bleeding disorder	1.53	1.25-1.86	<0.0001
Chronic respiratory disease	0.99	0.79-1.23	0.89
Functionally dependent	1.40	0.88-2.22	0.15
AIS head			<0.0001

3	Reference	NA	
4	1.70	1.34-2.16	
5	10.84	8.51-13.80	
GCS motor score			
1	3.31	2.64-4.14	<0.0001
2	3.11	2.28-4.24	
3	2.10	1.54-2.86	
4	1.29	0.99-1.68	
5	Reference	NA	
Hypotension (SBP<90)	4.60	3.09-6.59	<0.0001
Intracranial lesion			
Epidural hematoma	0.51	0.42-0.62	<0.0001
Subdural hematoma	0.97	0.85-1.10	0.58
Traumatic subarachnoid hemorrhage	1.18	1.06-1.32	0.003
Intracerebral mass lesion	1.52	1.23-1.88	0.0002
Compressed/absent basal cisterns	4.60	3.39-6.23	<0.0001
Brainstem/cerebellar lesion	1.61	1.35-1.92	<0.0001
Mechanism of injury			
Fall	Reference	NA	<0.0001
MVC	0.68	0.57-0.81	
Pedestrian	0.90	0.73-1.11	
Motorcycle	0.74	0.58-0.93	

Type of insurance			
Commercial vs. Non-commercial	0.91	0.81-1.04	0.32
Hospital-level characteristics			
Teaching status			
University	Reference	NA	0.81
Community	1.04	0.85-1.27	
Non-teaching	1.14	0.79-1.65	
No. of beds			
≤200	0.88	0.41-1.90	
201-400	0.84	0.59-1.18	0.46
401-600	0.96	0.72-1.28	
>600	Reference	NA	
Volume of TBI patients			
Quartile 1 (<24 patients)	Reference	NA	
Quartile 2 (25-57 patients)	0.72	0.42-1.24	0.01
Quartile 3 (58-95 patients)	0.63	0.39-1.03	
Quartile 4 (>96 patients)	0.48	0.30-0.78	

Odds ratios were estimated using a random-intercept multilevel model with ICP monitoring (patient-level variable) as the main exposure and in-hospital mortality as the outcome of interest.
ICP: intracranial pressure; IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; NA: not applicable.

Table 2.4: Baseline data of patients who were managed with and without intracranial pressure monitoring adjusted with the use of inverse probability weighting

Characteristic	ICP group (N=1,874)	No ICP group (N=8,754)	Standardized difference
Age-median (IQR)	49 (29-65)	51 (30-70)	0.04
Gender (%)			0.004
Female	28.7	28.5	
Race (%)			
Black	13.0	10.7	
White	70.6	71.9	0.07
Other race	12.1	12.6	
Unknown/missing	4.4	4.8	
Comorbid illnesses (%)			
Coronary artery disease	5.1	4.7	0.02
Hypertension	26.2	26.1	0.001
Diabetes	11.0	10.8	0.004
On dialysis	0.7	1.0	0.02
CVA with residual deficit	4.0	3.6	0.02
Cancer	0.4	1.2	0.09
Bleeding disorder	8.4	7.6	0.03
Chronic respiratory disease	4.9	5.4	0.02
Functionally dependent	1.8	1.1	0.06
AIS head (%)			
3	11.8	11.6	0.06

4	43.8	40.8	
5	44.5	47.6	
Intracranial lesion (%)			
Epidural hematoma	9.5	9.4	0.002
Subdural hematoma	61.1	62.7	0.03
Traumatic subarachnoid hemorrhage	51.5	48.6	0.06
Intracerebral mass lesion	5.1	5.5	0.02
Compressed/absent basal cisterns	3.0	3.3	0.02
Brainstem/cerebellar lesion	9.0	9.8	0.03
Hypotension (SBP <90) (%)	7.0	5.6	0.06
Motor GCS score-median (IQR)	1 (1-3)	1 (1-3)	0.01
Total GCS score-median (IQR)	3 (3-5)	3 (3-5)	0.01
Mechanism (%)			
Fall	48.4	52.4	0.09
Motor vehicle collision	18.8	17.2	
Motorcycle	6.4	6.3	
Pedestrian	7.6	7.9	
Other	18.9	16.3	
Type of insurance (%)			
Commercial	33.7	31.2	0.06
Non-commercial	57.9	60.5	
Unknown	8.3	8.3	

ICP: intracranial pressure; IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale

Table 2.5: The individual-level relationship between intracranial pressure monitoring and in-hospital mortality within each quartile of hospital-specific intracranial pressure monitoring use

Subgroup	Adjusted Odds Ratio	95% Confidence Interval
Quartile 1 (lowest)	0.72	0.60-0.86
Quartile 2	0.44	0.32-0.58
Quartile 3	0.69	0.51-0.91
Quartile 4 (highest)	0.49	0.34-0.72

Hospital-specific rates were categorized into lowest (quartile 1) to highest (quartile 4) quartiles based on the overall hospital-specific rate of ICP monitoring utilization during study period.

Table 3.1: Distributions of individual patients' characteristics[a]

Characteristic	Distribution
Age	Poisson distribution[b] with a mean age of 25 years. Minimum age was 16 and maximum was 99.
Gender	77% of patients are males.
GCS motor score	Poisson distribution[b] with a mean score of 3. Minimum score was 1 and maximum was 5.
Pupillary reactivity	Bilaterally reactive pupils in 82% of patients and one reactive pupil in 18%.
ICU length of stay	Poisson distribution[*] with a mean of 13 days for decompressive craniectomy and a mean of 18 days for barbiturate coma
Hospital length of stay	Poisson distribution[*] with a mean of 28 days for decompressive craniectomy and a mean of 37 days for barbiturate coma

[a] Distributions were selected to reflect the characteristics of severe traumatic brain injury patients who present with refractory intracranial hypertension; as described in previous studies of this patient population [129,186].
[b] Poisson distribution was chosen here to avoid sampling negative values for these parameters and ensure that only integer values are chosen.
GCS: Glasgow Coma Scale; ICU: intensive care unit

Table 3.2: Model variables, mean values and standard deviations

Parameter	Mean Value	Standard Deviation
Probabilities		
Death (GOS=1); decompressive craniectomy[129]	0.19	0.39
Unfavorable Outcome; decompressive craniectomy[129]	0.63	0.48
Vegetative (GOS=2)	0.24	0.43
Severe Disability (GOS=3)	0.76	0.43
Favorable Outcome; decompressive craniectomy[129]	0.37	0.48
Moderate Disability (GOS=4)	0.86	0.35
Good Recovery (GOS=5)	0.14	0.35
Hydrocephalus; decompressive craniectomy[129]	0.10	0.30
Perioperative hypotension; decompressive craniectomy[191]	0.31	0.46
Death (GOS=1); barbiturate coma[186]	0.60	0.49
Unfavorable Outcome; barbiturate coma[186]	0.29	0.45
Vegetative (GOS=2)	0.60	0.49
Severe Disability (GOS=3)	0.40	0.49
Favorable Outcome; barbiturate coma[186]	0.71	0.45
Moderate Disability (GOS=4)	0.50	0.50
Good Recovery (GOS=5)	0.50	0.50
Hydrocephalus; barbiturate coma[129]	0.01	0.30
Hypotension during barbiturate coma[132]	0.62	0.24
Failure of barbiturate therapy[186]	0.14	0.35
Perioperative mortality; ventriculoperitoneal shunt insertion[251]	0.02	0.14
Shunt Complications during first year[252]	0.25	0.43
Shunt Complications after first year[252]	0.02	0.14
Hazard ratio of long-term death for GOS=2-3[180]	1.79	0.27
Utility Values		
Death (GOS=1)[200]	0	-
Vegetative (GOS=2)	0	-
Severe Disability (GOS=3)[200]	0.15	0.06

Moderate Disability (GOS=4)[200]	0.51	0.06
Good Recovery (GOS=5)[200]	0.88	0.06
First month after decompressive craniectomy[a]	-0.01	0.46
First month after barbiturate coma[a]	-0.11	0.29
Month 2-6 after decompressive craniectomy[a]	0.56	0.33
Month 2-6 after barbiturate coma[a]	0.52	0.32
Disutility of permanent shunt[253]	-0.23	0.27
Disutility of ventriculoperitoneal shunt surgery[254]	-0.30	-
Disutility of shunt complication[254]	-0.40	-
Disutility of cranioplasty[a]	-0.42	0.45
Costs (US $)		
Decompressive craniectomy[204]	2,398.96	228.32
Cranioplasty[204]	1,059.48	99.13
Ventriculoperitoneal shunt insertion/revision[204]	1,073.09	99.12
ICU stay for severe TBI per day[202,203]	10,450.86	-
Medical-surgical floor stay for severe TBI per day[202,203]	3,483.62	-
Hospitalization for Ventriculoperitoneal shunt complication[205]	47,390.92	1,095.73
Rehabilitation cost for GOS=2-3[202,203]	17,320.75	-
Rehabilitation cost for GOS=4-5[202,203]	454.65	-
Nursing home per day[206]	207.06	34.03
Discount Rate		
Annual discount rate[209]	0.03	-

[a]The utility scores for temporary health states (within the first 6 months post-injury) were estimated by mapping those health states to the 5 domains of EQ-5D instrument by a panel of 12 neurosurgeons and intensivists. The mean quality of life scores were converted to utility scores using US population-based EQ-5D preference weights.[199]
GOS: Glasgow Outcome Scale; ICU: intensive care unit; TBI: traumatic brain injury.

Table 3.3: Comparison of Glasgow Outcome Scale scores between 1 and 5-7 years after traumatic brain injury[193]

GOS score at 1 year	GOS Score at 5-7 years (%)				
	1	2	3	4	5
1 (Death)	NA	NA	NA	NA	NA
2 (Vegetative)	100	0	0	0	0
3 (Severe Disability)	46	0	31	16	7
4 (Moderate Recovery)	30	0	6	41	23
5 (Good Recovery)	28	0	4	14	54

GOS: Glasgow Outcome Scale; NA: not applicable

Table 3.4: Proportion of traumatic brain injury patients who live in skilled nursing homes by Glasgow Outcome Scale category over time[a]

Year Since TBI	Proportion of Patients in Nursing Homes by GOS Score (%)			
	2 (Vegetative)	3 (Severe Disability)	4 (Moderate Recovery)	5 (Good Recovery)
Year 1	27	9	0.4	0.6
Year 2	25	11	0.2	0.1
Year 5	38	11	0.1	0.1
Year 10	18	13	0.3	0
Year 15	-	12	0	0

[a]Data derived from the Traumatic Brain Injury Model Systems National Database[207]
GOS: Glasgow Outcome Scale; TBI: traumatic brain injury

Table 3.5: Incremental cost-effectiveness of decompressive craniectomy relative to barbiturate coma for refractory intracranial hypertension following traumatic brain injury

Outcome	Decompressive Craniectomy	Barbiturate Coma
Discounted Cost (US $)-mean (SD)	132,564 (56,390)	117,780 (28,450)
Incremental Cost (US $)	14,784	-
Discounted QALM-mean (SD)	71.15 (29)	52.60 (22)
Incremental Effectiveness (QALM)	18.5	-
ICER (US $/QALY)	9,565	-
Mean Net Monetary Benefit (US $)[a]	163,891	101,393
Incremental Net Monetary Benefit (US $)[a]	62,498	-

[a]Calculated for a willingness-to-pay threshold of $50,000/QALY.
ICER: incremental cost-effectiveness ratio; QALM: quality-adjusted life months; QALY: quality-adjusted life years; SD: standard deviation.

Table 4.1: Baseline characteristics of patients who received early versus late tracheostomy

Characteristic	Early Tracheostomy (N=873)	Late Tracheostomy (N=938)	Standardized Difference
Age, median (IQR)	49 (30-64)	53 (35-68)	0.18
Gender, no. (%)			
Female	213 (24.4)	253 (27.0)	0.06
Race, no. (%)			
Black	117 (13.4)	149 (15.9)	
White	632 (72.4)	653 (69.6)	0.08
Other Race	96 (11.0)	102 (10.9)	
Unknown/missing	28 (3.2)	34 (3.6)	
Comorbid illnesses, no. (%)			
Coronary artery disease	27 (3.1)	56 (6.0)	0.14
Hypertension	242 (27.7)	307 (32.7)	0.11
Diabetes	105 (12.0)	159 (17.0)	0.14
On dialysis	6 (0.7)	8 (0.9)	0.02
CVA with residual deficit	29 (3.3)	45 (4.8)	0.07
Cancer	5 (0.6)	3 (0.3)	0.04
Bleeding disorder	52 (6.0)	85 (9.1)	0.12
Chronic respiratory disease	50 (5.7)	81 (8.6)	0.11
Functionally dependent	7 (0.8)	9 (1.0)	0.02
Current smoker	88 (10.1)	95 (10.1)	0.002
AIS head, no. (%)			
3	75 (8.6)	58 (6.2)	0.11
4	399 (45.7)	466 (49.7)	
5	399 (45.7)	414 (44.1)	
Intracranial lesion, no. (%)			

Epidural hematoma	84 (9.6)	90 (9.6)	0.001
Subdural hematoma	557 (63.8)	649 (69.2)	0.11
Traumatic subarachnoid hemorrhage	465 (53.3)	508 (54.2)	0.02
Intracerebral mass lesion	338 (38.7)	368 (39.2)	0.01
Compressed/absent basal cisterns	27 (3.1)	31 (3.3)	0.01
Brainstem/cerebellar lesion	78 (8.9)	82 (8.7)	0.01
Diffuse Axonal Injury	56 (6.4)	43 (4.6)	0.08
Hypotension (SBP <90), no. (%)	29 (3.3)	20 (2.1)	0.07
Missing SBP values, no. (%)	7 (0.8)	2 (0.2)	
Motor GCS score, median (IQR)	1 (1-5)	4 (1-6)	0.27
Total GCS score, median (IQR)	4 (3-10)	7 (3-13)	0.30
Mechanism, no. (%)			0.26
Fall	358 (41.0)	494 (52.7)	
Motor vehicle collision	189 (21.7)	164 (17.5)	
Motorcycle	96 (11.0)	57 (6.1)	
Pedestrian	83 (9.5)	79 (8.4)	
Other	147 (16.8)	144 (15.4)	
Type of insurance, no. (%)			0.12
Commercial	312 (35.7)	313 (33.4)	
Non-commercial	475 (54.4)	558 (59.5)	
Unknown	86 (9.9)	67 (7.1)	
Neurosurgical Procedure, no. (%)			
Craniotomy	289 (33.1)	343 (36.6)	0.07
ICP monitor insertion	309 (35.4)	346 (36.9)	0.03
Hospital type, no. (%)			0.06
Non-profit	835 (95.7)	884 (94.2)	

For profit	38 (4.4)	54 (5.8)	
No. of beds, no. (%)			
≤200	38 (4.4)	34 (3.6)	
201-400	163 (18.7)	165 (17.6)	0.14
401-600	268 (30.7)	240 (25.6)	
>600	404 (46.3)	499 (53.2)	
Teaching status, no. (%)			
University	546 (58.2)	500 (57.3)	0.03
Community	337 (38.6)	358 (38.2)	
Non-teaching	36 (4.1)	34 (3.6)	
Trauma center level, no. (%)			
Level I	695 (79.6)	759 (80.9)	0.03
Level II	178 (20.4)	179 (19.1)	
Volume of severe TBI patients, no. (%)			
Quartile 1 (<24 patients)	56 (6.4)	53 (5.7)	
Quartile 2 (25-57 patients)	169 (19.4)	165 (17.6)	0.12
Quartile 3 (58-95 patients)	254 (29.1)	325 (34.7)	
Quartile 4 (>96 patients)	394 (45.1)	395 (42.1)	

IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; ICP: intracranial pressure; TBI: traumatic brain injury.

Table 4.2: Baseline characteristics of patients who received early versus late tracheostomy after propensity-score matching

Characteristic	Early Tracheostomy (N=571)	Late Tracheostomy (N=571)	Standardized Difference
Age-median (IQR)	51 (31-65)	52 (35-65)	0.01
Gender, no. (%)			
Female	140 (24.5)	147 (25.7)	0.03
Race, no. (%)			
Black	79 (13.8)	81 (14.2)	
White	411 (72.0)	403 (70.6)	0.03
Other Race	63 (11.0)	68 (11.9)	
Unknown/missing	18 (3.2)	19 (3.3)	
Comorbid illnesses, no. (%)			
Coronary artery disease	23 (4.0)	29 (5.1)	0.05
Hypertension	179 (31.4)	179 (31.4)	0.00
Diabetes	83 (14.5)	89 (15.6)	0.03
On dialysis	5 (0.9)	3 (0.5)	0.04
CVA with residual deficit	18 (3.2)	19 (3.3)	0.01
Cancer	4 (0.7)	3 (0.5)	0.02
Bleeding disorder	37 (6.5)	41 (7.2)	0.03
Chronic respiratory disease	38 (6.7)	38 (6.7)	0.00
Functionally dependent	4 (0.7)	4 (0.7)	0.00
Current smoker	62 (10.9)	60 (10.5)	0.01
AIS head, no. (%)			
3	40 (7.0)	44 (7.7)	0.03
4	269 (47.1)	270 (47.3)	
5	262 (45.9)	257 (45.0)	
Intracranial lesion, no. (%)			

Epidural hematoma	58 (10.2)	60 (10.5)	0.01
Subdural hematoma	392 (68.7)	380 (66.6)	0.04
Traumatic subarachnoid hemorrhage	313 (54.8)	311 (54.5)	0.01
Intracerebral mass lesion	239 (41.9)	224 (39.2)	0.05
Compressed/absent basal cisterns	19 (3.3)	18 (3.2)	0.01
Brainstem/cerebellar lesion	42 (7.4)	45 (7.9)	0.01
Diffuse Axonal Injury	31 (5.4)	33 (5.8)	0.02
Hypotension (SBP <90), no. (%)	14 (2.5)	16 (2.8)	0.02
Motor GCS score, median (IQR)	3 (1-5)	3 (1-5)	0.01
Total GCS score, median (IQR)	6 (3-11)	6 (3-12)	0.04
Mechanism, no. (%)			
Fall	272 (47.6)	273 (47.8)	0.05
Motor vehicle collision	100 (17.5)	108 (18.9)	
Motorcycle	48 (8.4)	46 (8.1)	
Pedestrian	96 (16.8)	89 (15.6)	
Other	55 (9.6)	55 (9.6)	
Type of insurance, no. (%)			
Commercial	188 (32.9)	198 (34.7)	0.04
Non-commercial	333 (58.3)	328 (57.4)	
Unknown	50 (8.8)	45 (7.9)	
Neurosurgical Procedure, no. (%)			
Craniotomy	206 (36.1)	204 (35.7)	0.01
ICP monitor insertion	203 (35.6)	218 (38.2)	0.05
Hospital type, no. (%)			
Non-profit	538 (94.2)	544 (95.3)	0.05
For profit	33 (5.8)	27 (4.7)	

No. of beds, no. (%)			
≤200	24 (4.2)	26 (4.6)	
201-400	100 (17.5)	101 (17.7)	0.03
401-600	151 (26.4)	144 (25.2)	
>600	296 (51.8)	300 (52.5)	
Teaching status, no. (%)			
University	341 (29.9)	357 (31.3)	0.06
Community	207 (36.3)	190 (33.3)	
Non-teaching	23 (4.0)	24 (4.2)	
Trauma center level, no. (%)			
Level I	472 (82.7)	474 (83.0)	0.01
Level II	99 (17.3)	97 (17.0)	
Volume of severe TBI patients, no. (%)			
Quartile 1 (<24 patients)	27 (4.7)	26 (4.6)	
Quartile 2 (25-57 patients)	96 (16.8)	95 (16.6)	0.06
Quartile 3 (58-95 patients)	183 (32.1)	169 (29.6)	
Quartile 4 (>96 patients)	265 (46.4)	281 (49.2)	

IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; ICP: intracranial pressure; TBI: traumatic brain injury.

Table 4.3: Outcome distribution after propensity score matching

Outcome	Early Tracheostomy (N=571)	Late Tracheostomy (N=571)	Rate Ratio (95% CI)	P Value
Median ventilator days (IQR)	10 (7-15)	16 (12-21)	0.70 (0.66-0.75)	<0.0001
Median ICU days (IQR)	13 (10-18)	19 (15-25)	0.70 (0.66-0.75)	<0.0001
Median hospital days (IQR)	20 (15-29)	27 (20-38)	0.80 (0.74-0.86)	<0.0001

CI: confidence interval; IQR: interquartile range; ICU: intensive care unit

Table 4.4: Outcome frequency after propensity score matching

Outcome	Early Tracheostomy (N=571)	Late Tracheostomy (N=571)	Odds Ratio (95% CI)	Relative Risk (95% CI)	P Value
Pneumonia, no. (%)	238 (41.7)	301 (52.7)	0.64 (0.51-0.80)	0.79 (0.70-0.89)	0.0001
Deep venous thrombosis, no. (%)	47 (8.2)	82 (14.4)	0.53 (0.37-0.78)	0.57 (0.41-0.80)	0.001
Pulmonary embolism, no. (%)	10 (1.8)	19 (3.3)	0.52 (0.24-1.10)	0.53 (0.25-1.10)	0.09
Decubitus ulcer, no. (%)	23 (4.0)	51 (8.9)	0.43 (0.26-0.71)	0.45 (0.28-0.73)	0.001
Mortality, no. (%)	48 (8.4)	39 (6.8)	1.25 (0.80-1.96)	1.23 (0.81-1.86)	0.32

CI: confidence interval

Table 4.5: Outcome distribution after propensity score matching (excluding deaths)

Outcome	Early Tracheostomy (N=516)	Late Tracheostomy (N=516)	Rate Ratio (95% CI)	P Value
Median ventilator days (IQR)	10 (7-15)	16 (12-21)	0.70 (0.66-0.76)	<0.0001
Median ICU days (IQR)	13 (10-18)	18 (15-25)	0.70 (0.66-0.75)	<0.0001
Median hospital days (IQR)	20 (15-29)	27 (20-37)	0.80 (0.75-0.88)	<0.0001

CI: confidence interval; IQR: interquartile range; ICU: intensive care unit

Table 4.6: Outcome frequency after propensity score matching (excluding deaths)

Outcome	Early Tracheostomy (N=516)	Late Tracheostomy (N=516)	Odds Ratio (95% CI)	P Value
Pneumonia, no. (%)	213 (41.3)	281 (54.5)	0.59 (0.46-0.75)	<0.0001
Deep venous thrombosis, no. (%)	45 (8.7)	70 (13.6)	0.61 (0.41-0.90)	0.01
Pulmonary embolism, no. (%)	7 (1.4)	20 (3.9)	0.34 (0.14-0.82)	0.02
Decubitus ulcer, no. (%)	21 (4.1)	41 (8.0)	0.49 (0.29-0.83)	0.007

CI: confidence interval

Table 4.7: Results of multivariate proportional hazards regression considering tracheostomy timing as a time-dependent exposure

Outcome	Hazard Ratio (95% CI)*	P Value
Time to liberation from mechanical ventilation	2.04 (1.83-2.27)	<0.0001
Time to discharge from ICU	2.17 (1.91-2.48)	<0.0001
Time to discharge from hospital	1.65 (1.47-1.84)	<0.0001

*Hazard ratio compares early tracheostomy (≤8 days) with late tracheostomy (>8 days). Hazard ratio >1 implies that there is a higher likelihood of event (liberation from mechanical ventilation or discharge) with early tracheostomy.
CI: confidence interval; ICU: intensive care unit.

Table 4.8: Baseline characteristics of patients within strata based on hospital-specific rate of early tracheostomy utilization

Characteristic	Quartile 1 (N=344)	Quartile 2 (N=628)	Quartile 3 (N=430)	Quartile 4 (N=409)
Early Tracheostomy, no. (%)	70 (20.4)	265 (42.2)	240 (55.8)	298 (72.9)
Patient Characteristics				
Age, median (IQR)	53 (33-68)	51 (31-67)	51 (34-64)	50 (34-65)
Gender, no. (%)				
Female	99 (28.8)	163 (26.0)	96 (22.3)	108 (26.4)
Race, no. (%)				
Black	60 (17.4)	72 (11.5)	77 (17.9)	57 (13.9)
White	224 (65.1)	461 (73.4)	286 (66.5)	314 (76.8)
Other	32 (9.3)	80 (12.7)	61 (14.2)	25 (6.1)
Unknown/missing	28 (8.1)	15 (2.4)	6 (1.4)	13 (3.2)
Comorbid illnesses, no. (%)				
Coronary artery disease	20 (5.8)	33 (5.3)	14 (3.3)	16 (3.9)
Hypertension	123 (35.8)	191 (30.4)	120 (27.9)	115 (28.1)
Diabetes	56 (16.3)	92 (14.7)	60 (14.0)	56 (13.7)
On dialysis	3 (0.9)	5 (0.8)	3 (0.7)	3 (0.7)
CVA with residual deficit	18 (5.2)	25 (4.0)	21 (4.9)	10 (2.4)
Cancer	1 (0.3)	3 (0.5)	3 (0.7)	1 (0.2)
Bleeding disorder	35 (10.2)	46 (7.3)	25 (5.8)	31 (7.6)
Respiratory disease	20 (5.8)	52 (8.3)	25 (5.8)	34 (8.3)
Functionally dependent	5 (1.5)	5 (0.8)	3 (0.7)	3 (0.7)
AIS head, median (IQR)	4 (4-5)	4 (4-5)	4 (4-5)	4 (4-5)
Intracranial lesion, no. (%)				
Epidural hematoma	32 (9.3)	69 (11.0)	28 (6.5)	45 (11.0)
Subdural hematoma	228 (66.3)	442 (70.4)	270 (62.8)	266 (65.0)

Traumatic subarachnoid hemorrhage	187 (54.4)	351 (55.9)	236 (54.9)	199 (48.7)
Intracerebral mass lesion	122 (35.5)	273 (43.5)	165 (38.4)	146 (35.7)
Compressed/absent basal cisterns	19 (5.5)	19 (3.0)	6 (1.4)	14 (3.4)
Brainstem/cerebellar lesion	41 (11.9)	57 (9.1)	28 (6.5)	34 (8.3)
Diffuse Axonal Injury	20 (5.8)	39 (6.2)	24 (5.6)	16 (3.9)
Hypotension (SBP <90), no. (%)	6 (1.7)	16 (2.6)	9 (2.1)	18 (4.4)
Missing SBP values-no. (%)	3 (0.9)	2 (0.3)	1 (0.2)	3 (0.7)
Motor GCS score, median (IQR)	4 (1-6)	3 (1-5)	3 (1-5)	1 (1-5)
Total GCS score, median (IQR)	6 (3-13)	6 (3-12)	6 (3-12)	3 (3-11)
Mechanism, no. (%)				
Fall	165 (48.0)	292 (46.5)	203 (47.2)	192 (46.9)
Motor vehicle collision	60 (20.1)	110 (17.5)	88 (20.5)	86 (21.0)
Motorcycle	17 (4.9)	65 (10.4)	35 (8.1)	36 (8.8)
Pedestrian	33 (9.6)	49 (7.8)	44 (10.2)	36 (8.8)
Other	60 (17.4)	112 (17.8)	60 (14.0)	59 (14.4)
Type of insurance, no. (%)				
Commercial	124 (36.1)	198 (31.5)	165 (38.4)	138 (33.7)
Non-commercial	202 (58.7)	331 (52.7)	261 (60.7)	239 (58.4)
Unknown/missing	18 (5.2)	99 (15.8)	4 (0.9)	32 (7.8)
Neurosurgical procedure, no. (%)				
Craniotomy	145 (42.2)	243 (38.7)	130 (30.2)	114 (27.9)
ICP monitor insertion	111 (32.3)	217 (34.6)	186 (43.3)	141 (34.5)
Hospital type, no. (%)				
Non-profit	327 (95.1)	578 (92.0)	413 (96.1)	401 (98.0)
For profit	17 (4.9)	50 (8.0)	17 (4.0)	8 (2.0)
No. of beds, no. (%)				

≤200	0 (0.0)	23 (3.7)	42 (9.8)	7 (1.7)
201-400	57 (16.6)	143 (22.8)	33 (7.7)	95 (23.2)
401-600	89 (25.9)	181 (28.8)	47 (10.9)	191 (46.7)
>600	198 (57.6)	281 (44.8)	308 (71.6)	116 (28.4)
Teaching status, no. (%)				
University	179 (52.0)	362 (57.6)	303 (70.5)	202 (49.4)
Community	160 (46.5)	231 (36.8)	120 (27.9)	184 (45.0)
Non-teaching	5 (1.5)	35 (5.6)	7 (1.6)	23 (5.6)
Trauma center level, no. (%)				
Level I	265 (77.0)	496 (79.0)	380 (88.4)	313 (76.5)
Level II	79 (23.0)	132 (21.0)	50 (11.6)	96 (23.5)
Volume of severe TBI patients, no. (%)				
Quartile 1 (<24 patients)	20 (5.8)	50 (8.0)	5 (1.2)	24 (8.3)
Quartile 2 (25-57 patients)	84 (24.4)	112 (17.8)	26 (6.1)	112 (27.4)
Quartile 3 (58-95 patients)	148 (43.0)	189 (30.0)	122 (28.4)	120 (29.3)
Quartile 4 (>96 patients)	92 (26.7)	277 (44.1)	277 (64.4)	143 (35.0)

IQR: interquartile range; CVA: cerebrovascular accident; AIS: abbreviated injury scale; SBP: systolic blood pressure; GCS: Glasgow Coma Scale; ICP: intracranial pressure; traumatic brain injury.

Table 4.9: Adjusted hospital-level analysis of the relationship between tracheostomy timing and outcome

Hospital Quartile	Early Tracheostomy Rate	Rate Ratio (95% CI)		
		Mechanical Ventilator Days	ICU Length of Stay	Hospital Length of Stay
Quartile 4 (Highest)	>64%	0.67 (0.60-0.74)	0.68 (0.62-0.76)	0.70 (0.62-0.79)
Quartile 3	51-64%	0.79 (0.69-0.89)	0.78 (0.70-0.87)	0.83 (0.72-0.96)
Quartile 2	30-50%	0.81 (0.73-0.91)	0.83 (0.76-0.91)	0.86 (0.77-0.96)
Quartile 1 (Lowest)	0-29%	Reference	Reference	Reference

Quartile 4 has the highest hospital-specific rate of early tracheostomy for traumatic brain injury patients and Quartile 1 (the reference) has the lowest.
CI: confidence interval; ICU: intensive care unit

Table 4.10: Adjusted analysis of the relationship between tracheostomy timing quartiles and outcome

Tracheostomy Timing Quartile	Rate Ratio (95% CI)		
	Mechanical Ventilator Days	ICU Length of Stay	Hospital Length of Stay
Quartile 1 (<6 days): 425 patients	0.56 (0.52-0.61)	0.58 (0.53-0.63)	0.65 (0.60-0.70)
Quartile 2 (6-<9 days): 448 patients	0.67 (0.62-0.71)	0.66 (0.62-0.70)	0.74 (0.69-0.80)
Quartile 3 (9-<12 days): 424 patients	0.80 (0.74-0.85)	0.76 (0.72-0.80)	0.89 (0.75-0.85)
Quartile 4 (≥12 days): 514 patients	Reference	Reference	Reference

CI: confidence interval; ICU: intensive care unit.

REFERENCES

1. Azevedo FA, Carvalho LR, Grinberg LT, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *The Journal of comparative neurology.* Apr 10 2009;513(5):532-541.
2. Rose FD, Johnson DA. *Brain Injury and After: Towards Improved Outcome.* John Wiley & Sons Canada, Ltd.; 1996.
3. Kandel ER, Schwartz JH, Jessel TM. *Principles of Neural Science.* Fourth ed: McGraw-Hill Medical; 2000.
4. Toro R, Perron M, Pike B, et al. Brain size and folding of the human cerebral cortex. *Cerebral cortex.* Oct 2008;18(10):2352-2357.
5. Brodmann K. *Vergleichende Lokalisationslehre der Gro sshirnrinde.* Leipzig: Verlag von Johann Ambrosius Barth; 1909.
6. Terminology FCoA. *Terminologia Anatomica: International Anatomical Terminology.* Thieme Stuttgart; 1998.
7. Ribas GC. The cerebral sulci and gyri. *Neurosurgical focus.* Feb 2010;28(2):E2.
8. Afifi A, Bergman R. *Functional Neuroanatomy: Text and Atlas.* Second ed: McGraw-Hill Medical; 2005.
9. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nature neuroscience.* Feb 2004;7(2):189-195.
10. Craig AD. How do you feel--now? The anterior insula and human awareness. *Nature reviews. Neuroscience.* Jan 2009;10(1):59-70.
11. Ramirez-Amaya V, Bermudez-Rattoni F. Conditioned enhancement of antibody production is disrupted by insular cortex and amygdala but not hippocampal lesions. *Brain, behavior, and immunity.* Mar 1999;13(1):46-60.
12. Price CJ. The anatomy of language: contributions from functional neuroimaging. *Journal of anatomy.* Oct 2000;197 Pt 3:335-359.
13. Lord LD, Expert P, Huckins JF, Turkheimer FE. Cerebral energy metabolism and the brain's functional network architecture: an integrative review. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism.* Sep 2013;33(9):1347-1354.
14. Siegel GJ, Agranoff BW, Albers RW, Price D. *Basic Neurochemistry: Principles of Molecular, Cellular, and Medical Neurobiology.* Sixth ed. Philadelphia: Lippincott-Raven; 1999.
15. Shahlaie K, Zwienenberg-Lee M, Muizelaar JP. Clinical Pathophysiology of Traumatic Brain Injury. In: Winn HR, ed. *Youmans Neurological Surgery.* Vol 4. Sixth ed: Saunders; 2011.
16. Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. *Glia.* Sep 2007;55(12):1263-1271.
17. Quistorff B, Secher NH, Van Lieshout JJ. Lactate fuels the human brain during exercise. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* Oct 2008;22(10):3443-3449.

18. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF, Jr. Brain metabolism during fasting. *The Journal of clinical investigation.* Oct 1967;46(10):1589-1595.
19. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL, Jr. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *The American journal of physiology.* Apr 1978;234(4):H371-383.
20. Faraci FM, Heistad DD. Regulation of the cerebral circulation: role of endothelium and potassium channels. *Physiological reviews.* Jan 1998;78(1):53-97.
21. Thurman DJ, Sniezek JE, Johnson D, Greenspan A, Smith SM. *Guidelines for Surveillance of Central Nervous System Injury.* Atlanta, GA: Centers for Disease Control and Prevention; 1995.
22. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet neurology.* Aug 2008;7(8):728-741.
23. Schouten J, Maas AI. Epidemiology of Traumatic Brain Injury. In: Winn HR, ed. *Youmans Neurological Surgery.* Vol 4. Sixth ed: Saunders; 2011.
24. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* Jul 13 1974;2(7872):81-84.
25. Stocchetti N, Pagan F, Calappi E, et al. Inaccurate early assessment of neurological severity in head injury. *J Neurotrauma.* Sep 2004;21(9):1131-1140.
26. Marshall LF, Marshall SB, Klauber MR. A new classification of head injury based on computerized tomography. *Journal of neurosurgery.* 1991;75(Supplement):S14-20.
27. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery.* Dec 2005;57(6):1173-1182; discussion 1173-1182.
28. Gennarelli TA, Champion HR, Sacco WJ, Copes WS, Alves WM. Mortality of patients with head injury and extracranial injury treated in trauma centers. *The Journal of trauma.* Sep 1989;29(9):1193-1201; discussion 1201-1192.
29. Committee on Injury Scaling (1998). The Abbreviated Injury Scale, 1998 revision (AIS-98). Association for the Advancement of Automotive Medicine: Des Plaines (IL).
30. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *J Neurotrauma.* Aug 2010;27(8):1529-1540.
31. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *The Journal of trauma.* Feb 1993;34(2):216-222.
32. Hovda DA, Becker DP, Katayama Y. Secondary injury and acidosis. *J Neurotrauma.* Mar 1992;9 Suppl 1:S47-60.
33. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *Journal of neurosurgery.* Dec 1990;73(6):889-900.

34. Zacko JC, Hawryluk GW, Bullock MR. Neurochemical Pathomechanisms in Traumatic Brain Injury. In: Winn HR, ed. *Youmans Neurological Surgery.* Vol 4. Sixth ed: Saunders; 2011.
35. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *J Neurotrauma.* 2007;24 Suppl 1:S71-76.
36. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma.* 2007;24 Suppl 1:S7-13.
37. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. *J Neurotrauma.* 2007;24 Suppl 1:S65-70.
38. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma.* 2007;24 Suppl 1:S59-64.
39. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma.* 2007;24 Suppl 1:S55-58.
40. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma.* 2007;24 Suppl 1:S14-20.
41. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology.* Jul 1989;15(1):49-59.
42. Graham DI. The pathology of brain ischaemia and possibilities for therapeutic intervention. *British journal of anaesthesia.* Jan 1985;57(1):3-17.
43. Marmarou A. Traumatic brain edema: an overview. *Acta neurochirurgica. Supplementum.* 1994;60:421-424.
44. Marmarou A, Signoretti S, Fatouros PP, Portella G, Aygok GA, Bullock MR. Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries. *Journal of neurosurgery.* May 2006;104(5):720-730.
45. Choi DW. Calcium: still center-stage in hypoxic-ischemic neuronal death. *Trends in neurosciences.* Feb 1995;18(2):58-60.
46. Bergsneider M, Hovda DA, Shalmon E, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *Journal of neurosurgery.* Feb 1997;86(2):241-251.
47. Kontos HA, Povlishock JT. Oxygen radicals in brain injury. *Central nervous system trauma : journal of the American Paralysis Association.* Fall 1986;3(4):257-263.
48. Hall ED, Braughler JM. Central nervous system trauma and stroke. II. Physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation. *Free radical biology & medicine.* 1989;6(3):303-313.
49. Soares HD, Hicks RR, Smith D, McIntosh TK. Inflammatory leukocytic recruitment and diffuse neuronal degeneration are separate pathological processes resulting from traumatic brain injury. *The Journal of neuroscience :*

the official journal of the Society for Neuroscience. Dec 1995;15(12):8223-8233.
50. Giulian D, Chen J, Ingeman JE, George JK, Noponen M. The role of mononuclear phagocytes in wound healing after traumatic injury to adult mammalian brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* Dec 1989;9(12):4416-4429.
51. Talley AK, Dewhurst S, Perry SW, et al. Tumor necrosis factor alpha-induced apoptosis in human neuronal cells: protection by the antioxidant N-acetylcysteine and the genes bcl-2 and crmA. *Molecular and cellular biology.* May 1995;15(5):2359-2366.
52. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. *Journal of neurosurgery.* Mar 1991;74(3):407-414.
53. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. *Journal of neurosurgery.* Aug 1984;61(2):241-253.
54. Fieschi C, Battistini N, Beduschi A, Boselli L, Rossanda M. Regional cerebral blood flow and intraventricular pressure in acute head injuries. *Journal of neurology, neurosurgery, and psychiatry.* Dec 1974;37(12):1378-1388.
55. Muizelaar JP, Lutz HA, 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *Journal of neurosurgery.* Oct 1984;61(4):700-706.
56. Ellis EF, Dodson LY, Police RJ. Restoration of cerebrovascular responsiveness to hyperventilation by the oxygen radical scavenger n-acetylcysteine following experimental traumatic brain injury. *Journal of neurosurgery.* Nov 1991;75(5):774-779.
57. Kontos HA, Wei EP. Oxygen-dependent mechanisms in cerebral autoregulation. *Annals of biomedical engineering.* 1985;13(3-4):329-334.
58. Lewelt W, Jenkins LW, Miller JD. Effects of experimental fluid-percussion injury of the brain on cerebrovascular reactivity of hypoxia and to hypercapnia. *Journal of neurosurgery.* Mar 1982;56(3):332-338.
59. Marmarou A, Maset AL, Ward JD, et al. Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients. *Journal of neurosurgery.* Jun 1987;66(6):883-890.
60. Monro A. Observations on structure and functions of the nervous system. Edinburgh: Creech and Johnson; 1783.
61. Kellie G. Appearances observed in the dissection of two individuals; death from cold and congestion of the brain. Vol 1. Edinburgh: Trans Med-Chir Soc; 1824.
62. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology.* Jun 26 2001;56(12):1746-1748.
63. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *Journal of neurosurgery.* 1991;75(1S):S59-S66.

64. Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. *Neurocritical care.* 2007;6(2):104-112.
65. Robertson C, Rangel-Castilla L. Critical Care Management of Traumatic Brain Injury. In: Winn HR, ed. *Youmans Neurological Surgery.* Vol 4. Sixth ed: Saunders; 2011.
66. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta neurochirurgica. Supplementum.* 1993;59:121-125.
67. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Archives of surgery.* Oct 2001;136(10):1118-1123.
68. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS medicine.* Aug 5 2008;5(8):e165; discussion e165.
69. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. *Journal of neurosurgical anesthesiology.* Jan 1994;6(1):4-14.
70. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *The Journal of trauma.* May 1996;40(5):764-767.
71. Van Beek JG, Mushkudiani NA, Steyerberg EW, et al. Prognostic value of admission laboratory parameters in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* Feb 2007;24(2):315-328.
72. Behr R, Erlingspiel D, Becker A. Early and longtime modifications of temperature regulation after severe head injury. Prognostic implications. *Annals of the New York Academy of Sciences.* Mar 15 1997;813:722-732.
73. Dietrich WD. The importance of brain temperature in cerebral injury. *J Neurotrauma.* May 1992;9 Suppl 2:S475-485.
74. Thompson HJ, Tkacs NC, Saatman KE, Raghupathi R, McIntosh TK. Hyperthermia following traumatic brain injury: a critical evaluation. *Neurobiology of disease.* Apr 2003;12(3):163-173.
75. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C. Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma.* Jul 2002;19(7):869-874.
76. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Critical care medicine.* Jul 2004;32(7):1489-1495.
77. Malkinson TJ, Veale WL, Cooper KE. Fever and intracranial pressures. *Brain research bulletin.* Sep 1985;15(3):315-319.
78. Stocchetti N, Protti A, Lattuada M, et al. Impact of pyrexia on neurochemistry and cerebral oxygenation after acute brain injury. *Journal of neurology, neurosurgery, and psychiatry.* Aug 2005;76(8):1135-1139.

79. Meldrum BS, Nilsson B. Cerebral blood flow and metabolic rate early and late in prolonged epileptic seizures induced in rats by bicuculline. *Brain : a journal of neurology.* Sep 1976;99(3):523-542.
80. Vespa P, Prins M, Ronne-Engstrom E, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. *Journal of neurosurgery.* Dec 1998;89(6):971-982.
81. Porta M. *A Dictionary of Epidemiology.* Fifth ed: Oxford University Press; 2008.
82. Bruns J, Jr., Hauser WA. The epidemiology of traumatic brain injury: a review. *Epilepsia.* 2003;44 Suppl 10:2-10.
83. Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: prospective cohort study. *BMJ.* Jun 17 2000;320(7250):1631-1635.
84. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nature medicine.* Nov 1998;4(11):1241-1243.
85. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of head trauma rehabilitation.* Sep-Oct 2006;21(5):375-378.
86. Faul M, Wald MM, Xu L, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002-2006. *Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.* 2010.
87. Finkelstein EA CP, Miller TR. *The Incidence and Economic Burden of Injuries in the United States.* New York (NY): Oxford University Press; 2006.
88. Zygun DA, Laupland KB, Hader WJ, et al. Severe traumatic brain injury in a large Canadian health region. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques.* Feb 2005;32(1):87-92.
89. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta neurochirurgica.* Mar 2006;148(3):255-268; discussion 268.
90. Mushkudiani NA, Engel DC, Steyerberg EW, et al. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. *J Neurotrauma.* Feb 2007;24(2):259-269.
91. Slaughter B, Fann JR, Ehde D. Traumatic brain injury in a county jail population: prevalence, neuropsychological functioning and psychiatric disorders. *Brain injury : [BI].* Sep 2003;17(9):731-741.
92. Ivins BJ, Schwab KA, Warden D, et al. Traumatic brain injury in U.S. Army paratroopers: prevalence and character. *The Journal of trauma.* Oct 2003;55(4):617-621.
93. Andriessen TM, Horn J, Franschman G, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma.* Oct 2011;28(10):2019-2031.
94. Stocchetti N, Paterno R, Citerio G, Beretta L, Colombo A. Traumatic brain injury in an aging population. *J Neurotrauma.* Apr 10 2012;29(6):1119-1125.

95. Adekoya N, Majumder R. Fatal traumatic brain injury, West Virginia, 1989-1998. *Public health reports.* Sep-Oct 2004;119(5):486-492.
96. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *The Journal of head trauma rehabilitation.* Nov-Dec 2006;21(6):544-548.
97. Adekoya N, Thurman DJ, White DD, Webb KW. Surveillance for traumatic brain injury deaths--United States, 1989-1998. *MMWR Surveill Summ.* Dec 6 2002;51(10):1-14.
98. Jager TE, Weiss HB, Coben JH, Pepe PE. Traumatic brain injuries evaluated in U.S. emergency departments, 1992-1994. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* Feb 2000;7(2):134-140.
99. Kraus JF, Black MA, Hessol N, et al. The incidence of acute brain injury and serious impairment in a defined population. *American journal of epidemiology.* Feb 1984;119(2):186-201.
100. Durkin MS, Olsen S, Barlow B, Virella A, Connolly ES, Jr. The epidemiology of urban pediatric neurological trauma: evaluation of, and implications for, injury prevention programs. *Neurosurgery.* Feb 1998;42(2):300-310.
101. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet.* Sep 22 2012;380(9847):1088-1098.
102. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation.* 2007;22(5):341-353.
103. Donabedian A. Evaluating the quality of medical care. *The Milbank Memorial Fund quarterly.* Jul 1966;44(3):Suppl:166-206.
104. Donabedian A. *An Introduction to Quality Assurance in Health Care.* New York: Oxford University Press; 2003.
105. Selhorst JB, Gudeman SK, Butterworth JFt, Harbison JW, Miller JD, Becker DP. Papilledema after acute head injury. *Neurosurgery.* Mar 1985;16(3):357-363.
106. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VII. Intracranial pressure monitoring technology. *J Neurotrauma.* 2007;24 Suppl 1:S45-54.
107. Stocchetti N, Zanaboni C, Colombo A, et al. Refractory intracranial hypertension and "second-tier" therapies in traumatic brain injury. *Intensive care medicine.* Mar 2008;34(3):461-467.
108. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. *Acta neurochirurgica.* 1989;100(1-2):12-24.
109. Koh WY, Lew TW, Chin NM, Wong MF. Tracheostomy in a neuro-intensive care setting: indications and timing. *Anaesthesia and intensive care.* Aug 1997;25(4):365-368.
110. Bouderka MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. *The Journal of trauma.* Aug 2004;57(2):251-254.

111. Scales DC, Ferguson ND. Early vs late tracheotomy in ICU patients. *JAMA : the journal of the American Medical Association.* Apr 21 2010;303(15):1537-1538.
112. Chuang K, Stroud NL, Zafonte R. Rehabilitation of Patients with Traumatic Brain Injury. In: Winn HR, ed. *Youmans Neurological Surgery.* Vol 4. Sixth ed: Saunders; 2011.
113. Kurien M, McAlindon ME, Westaby D, Sanders DS. Percutaneous endoscopic gastrostomy (PEG) feeding. *BMJ.* 2010;340:c2414.
114. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. *J Neurotrauma.* 2007;24 Suppl 1:S37-44.
115. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. *Journal of neurosurgery.* Oct 1977;47(4):491-502.
116. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ. Significance of intracranial hypertension in severe head injury. *Journal of neurosurgery.* Oct 1977;47(4):503-516.
117. Narayan RK, Greenberg RP, Miller JD, et al. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. *Journal of neurosurgery.* Jun 1981;54(6):751-762.
118. Bulger EM, Nathens AB, Rivara FP, Moore M, MacKenzie EJ, Jurkovich GJ. Management of severe head injury: institutional variations in care and effect on outcome. *Critical care medicine.* Aug 2002;30(8):1870-1876.
119. Lane PL, Skoretz TG, Doig G, Girotti MJ. Intracranial pressure monitoring and outcomes after traumatic brain injury. *Canadian journal of surgery. Journal canadien de chirurgie.* Dec 2000;43(6):442-448.
120. Farahvar A, Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *Journal of neurosurgery.* Oct 2012;117(4):729-734.
121. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. *The Journal of trauma.* Feb 2008;64(2):335-340.
122. Chesnut RM. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. *The Journal of trauma.* Aug 2008;65(2):500-501.
123. Maas AI, Schouten JW, Stocchetti N, Bullock R, Ghajar J. Questioning the value of intracranial pressure (ICP) monitoring in patients with brain injuries. *The Journal of trauma.* Oct 2008;65(4):966-967.
124. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *The New England journal of medicine.* Dec 27 2012;367(26):2471-2481.
125. Badri S, Chen J, Barber J, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. *Intensive care medicine.* Nov 2012;38(11):1800-1809.

126. Hutchinson PJ, Kolias AG, Czosnyka M, Kirkpatrick PJ, Pickard JD, Menon DK. Intracranial pressure monitoring in severe traumatic brain injury. *BMJ.* 2013;346:f1000.
127. Chesnut R, Celix JM, Chaddock K, et al. Outcome from severe traumatic brain in Latin America: Results from the Latin American pilot traumatic coma databank. *J Neurotrauma.* 2011;28(6):A111-A112.
128. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery.* Mar 2006;58(3 Suppl):S25-46; discussion Si-iv.
129. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *The New England journal of medicine.* Apr 21 2011;364(16):1493-1502.
130. Honeybul S, Ho KM, Lind CR. What can be learned from the DECRA study. *World neurosurgery.* Jan 2013;79(1):159-161.
131. Kitagawa RS, Bullock MR. Lessons from the DECRA study. *World neurosurgery.* Jan 2013;79(1):82-84.
132. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *Journal of neurosurgery.* Jul 1988;69(1):15-23.
133. Fearnside MR, Cook RJ, McDougall P, McNeil RJ. The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical and CT variables. *British journal of neurosurgery.* 1993;7(3):267-279.
134. Young D, Harrison DA, Cuthbertson BH, Rowan K. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *JAMA : the journal of the American Medical Association.* May 22 2013;309(20):2121-2129.
135. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Apr 21 2010;303(15):1483-1489.
136. Ahmed N, Kuo YH. Early versus late tracheostomy in patients with severe traumatic head injury. *Surgical infections.* Jun 2007;8(3):343-347.
137. Gandia-Martinez F, Martinez-Gil I, Andaluz-Ojeda D, Bobillo de Lamo F, Parra-Morais L, Diez-Gutierrez F. [Analysis of early tracheostomy and its impact on development of pneumonia, use of resources and mortality in neurocritically ill patients]. *Neurocirugia (Astur).* Jun 2010;21(3):211-221.
138. Rizk EB, Patel AS, Stetter CM, Chinchilli VM, Cockroft KM. Impact of tracheostomy timing on outcome after severe head injury. *Neurocritical care.* Dec 2011;15(3):481-489.
139. Sugerman HJ, Wolfe L, Pasquale MD, et al. Multicenter, randomized, prospective trial of early tracheostomy. *The Journal of trauma.* Nov 1997;43(5):741-747.
140. Wang HK, Lu K, Liliang PC, et al. The impact of tracheostomy timing in patients with severe head injury: an observational cohort study. *Injury.* Sep 2012;43(9):1432-1436.

141. Goettler CE, Fugo JR, Bard MR, et al. Predicting the need for early tracheostomy: a multifactorial analysis of 992 intubated trauma patients. *The Journal of trauma.* May 2006;60(5):991-996.
142. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. *Neurocritical care.* Dec 2009;11(3):417-426.
143. Needham DM, Dowdy DW, Mendez-Tellez PA, Herridge MS, Pronovost PJ. Studying outcomes of intensive care unit survivors: measuring exposures and outcomes. *Intensive care medicine.* Sep 2005;31(9):1153-1160.
144. Sahuquillo J, Arikan F. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. *Cochrane Database Syst Rev.* 2006(1):CD003983.
145. Park E, Bell JD, Baker AJ. Traumatic brain injury: can the consequences be stopped? *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Apr 22 2008;178(9):1163-1170.
146. Guillaume J, Janny P. [Continuous intracranial manometry; importance of the method and first results]. *Revue neurologique.* Feb 1951;84(2):131-142.
147. Padayachy LC, Figaji AA, Bullock MR. Intracranial pressure monitoring for traumatic brain injury in the modern era. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Apr 2010;26(4):441-452.
148. Carney N, Lujan S, Dikmen S, et al. Intracranial pressure monitoring in severe traumatic brain injury in latin america: process and methods for a multi-center randomized controlled trial. *J Neurotrauma.* Jul 20 2012;29(11):2022-2029.
149. Saul TG, Ducker TB. Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. *Journal of neurosurgery.* Apr 1982;56(4):498-503.
150. Biersteker HA, Andriessen TM, Horn J, et al. Factors influencing intracranial pressure monitoring guideline compliance and outcome after severe traumatic brain injury. *Critical care medicine.* Jun 2012;40(6):1914-1922.
151. Cremer OL, van Dijk GW, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Critical care medicine.* Oct 2005;33(10):2207-2213.
152. Harris OA, Bruce CA, Reid M, et al. Examination of the management of traumatic brain injury in the developing and developed world: focus on resource utilization, protocols, and practices that alter outcome. *Journal of neurosurgery.* Sep 2008;109(3):433-438.
153. Salim A, Hannon M, Brown C, et al. Intracranial pressure monitoring in severe isolated pediatric blunt head trauma. *The American surgeon.* Nov 2008;74(11):1088-1093.
154. Mauritz W, Steltzer H, Bauer P, Dolanski-Aghamanoukjan L, Metnitz P. Monitoring of intracranial pressure in patients with severe traumatic brain injury: an Austrian prospective multicenter study. *Intensive care medicine.* Jul 2008;34(7):1208-1215.
155. Sahjpaul R, Girotti M. Intracranial pressure monitoring in severe traumatic brain injury--results of a Canadian survey. *The Canadian journal of*

neurological sciences. Le journal canadien des sciences neurologiques. May 2000;27(2):143-147.
156. Murray LS, Teasdale GM, Murray GD, Miller DJ, Pickard JD, Shaw MD. Head injuries in four British neurosurgical centres. *British journal of neurosurgery.* Dec 1999;13(6):564-569.
157. Clifton GL, Choi SC, Miller ER, et al. Intercenter variance in clinical trials of head trauma--experience of the National Acute Brain Injury Study: Hypothermia. *Journal of neurosurgery.* Nov 2001;95(5):751-755.
158. Lingsma HF, Roozenbeek B, Li B, et al. Large between-center differences in outcome after moderate and severe traumatic brain injury in the international mission on prognosis and clinical trial design in traumatic brain injury (IMPACT) study. *Neurosurgery.* Mar 2011;68(3):601-607; discussion 607-608.
159. Lingsma HF, Roozenbeek B, Perel P, Roberts I, Maas AI, Steyerberg EW. Between-centre differences and treatment effects in randomized controlled trials: a case study in traumatic brain injury. *Trials.* 2011;12:201.
160. Hemmila MR, Nathens AB, Shafi S, et al. The Trauma Quality Improvement Program: pilot study and initial demonstration of feasibility. *The Journal of trauma.* Feb 2010;68(2):253-262.
161. Shafi S, Nathens AB, Cryer HG, et al. The Trauma Quality Improvement Program of the American College of Surgeons Committee on Trauma. *Journal of the American College of Surgeons.* Oct 2009;209(4):521-530 e521.
162. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ.* Apr 23 2005;330(7497):960-962.
163. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS®. *SAS proceedings.* 2012.
164. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *American journal of epidemiology.* Jan 1989;129(1):125-137.
165. Mittlbock M, Schemper M. Explained variation for logistic regression. *Statistics in medicine.* Oct 15 1996;15(19):1987-1997.
166. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *Journal of epidemiology and community health.* Apr 2006;60(4):290-297.
167. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *American journal of epidemiology.* Jan 1 2005;161(1):81-88.
168. Wijeysundera DN, Austin PC, Beattie WS, Hux JE, Laupacis A. Variation in the practice of preoperative medical consultation for major elective noncardiac surgery: a population-based study. *Anesthesiology.* Jan 2012;116(1):25-34.
169. Merlo J, Yang M, Chaix B, Lynch J, Rastam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: investigating contextual phenomena in different groups of people. *Journal of epidemiology and community health.* Sep 2005;59(9):729-736.

170. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Statistics in medicine.* Oct 15 2004;23(19):2937-2960.
171. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Statistics in medicine.* Sep 10 2010;29(20):2137-2148.
172. Finney JW, Humphreys K, Kivlahan DR, Harris AH. Why health care process performance measures can have different relationships to outcomes for patients and hospitals: understanding the ecological fallacy. *American journal of public health.* Sep 2011;101(9):1635-1642.
173. Chesnut RM, Temkin N, Carney N, et al. Traumatic brain injury in Latin America: lifespan analysis randomized control trial protocol*. *Neurosurgery.* Dec 2012;71(6):1055-1063.
174. Akopian G, Gaspard DJ, Alexander M. Outcomes of blunt head trauma without intracranial pressure monitoring. *The American surgeon.* May 2007;73(5):447-450.
175. Citerio G, Stocchetti N. Intracranial pressure and outcome in severe traumatic brain injury: the quest for evidence continues. *Intensive care medicine.* Jul 2008;34(7):1173-1174.
176. Turgeon AF, Lauzier F, Simard JF, et al. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* Oct 4 2011;183(14):1581-1588.
177. Pazzaglia P, Frank G, Frank F, Gaist G. Clinical course and prognosis of acute post-traumatic coma. *Journal of neurology, neurosurgery, and psychiatry.* Feb 1975;38(2):149-154.
178. Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. *Journal of neurosurgery.* May 2010;112(5):1105-1112.
179. Colantonio A, Escobar MD, Chipman M, et al. Predictors of postacute mortality following traumatic brain injury in a seriously injured population. *The Journal of trauma.* Apr 2008;64(4):876-882.
180. Selassie AW, McCarthy ML, Ferguson PL, Tian J, Langlois JA. Risk of posthospitalization mortality among persons with traumatic brain injury, South Carolina 1999-2001. *The Journal of head trauma rehabilitation.* May-Jun 2005;20(3):257-269.
181. Majdan M, Mauritz W, Brazinova A, Wilbacher I, Rusnak M, Leitgeb J. Barbiturates use and its effects in patients with severe TBI in five European countries. *J Neurotrauma.* Sep 5 2012.
182. Committee on Injury Scaling. *The Abbreviated Injury Scale, 1998 revision (AIS-98).* Des Plaines, IL: Association for the Advancement of Automotive Medicine; 1998.

183. Cooper DJ, Rosenfeld JV. Does decompressive craniectomy improve outcomes in patients with diffuse traumatic brain injury? *Med J Aust.* May 2 2011;194(9):437-438.
184. Schneider GH, Bardt T, Lanksch WR, Unterberg A. Decompressive craniectomy following traumatic brain injury: ICP, CPP and neurological outcome. *Acta Neurochir Suppl.* 2002;81:77-79.
185. Roberts I. Barbiturates for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000(2):CD000033.
186. Perez-Barcena J, Llompart-Pou JA, Homar J, et al. Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial. *Crit Care.* 2008;12(4):R112.
187. Caro JJ, Briggs AH, Siebert U, Kuntz KM, Force I-SMGRPT. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Sep-Oct 2012;15(6):796-803.
188. Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Sep-Oct 2012;15(6):804-811.
189. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Sep-Oct 2012;15(6):812-820.
190. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Sep-Oct 2012;15(6):835-842.
191. Albanese J, Leone M, Alliez JR, et al. Decompressive craniectomy for severe traumatic brain injury: Evaluation of the effects at one year. *Critical care medicine.* Oct 2003;31(10):2535-2538.
192. Hukkelhoven CW, Steyerberg EW, Rampen AJ, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *Journal of neurosurgery.* Oct 2003;99(4):666-673.
193. Whitnall L, McMillan TM, Murray GD, Teasdale GM. Disability in young people and adults after head injury: 5-7 year follow up of a prospective cohort study. *Journal of neurology, neurosurgery, and psychiatry.* May 2006;77(5):640-645.
194. Arias E. United States Life Tables, 2008. *National Vital Statistics Reports* 2012; http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_03.pdf. Accessed December 1, 2012.
195. Strauss DJ, Shavelle RM, Ashwal S. Life expectancy and median survival time in the permanent vegetative state. *Pediatric neurology.* Sep 1999;21(3):626-631.

196. Harrison-Felix C, Whiteneck G, DeVivo M, Hammond FM, Jha A. Mortality following rehabilitation in the Traumatic Brain Injury Model Systems of Care. *NeuroRehabilitation.* 2004;19(1):45-54.
197. Torrance GW. Utility approach to measuring health-related quality of life. *Journal of chronic diseases.* 1987;40(6):593-603.
198. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Annals of medicine.* Jul 2001;33(5):337-343.
199. Shaw JW, Pickard AS, Yu S, et al. A median model for predicting United States population-based EQ-5D health state preferences. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* Mar-Apr 2010;13(2):278-288.
200. Smits M, Dippel DWJ, Nederkoorn PJ, et al. Minor head injury: CT-based strategies for management--a cost-effectiveness analysis. *Radiology.* Feb 2010;254(2):532-540.
201. Smits M, Hunink MG, van Rijssel DA, et al. Outcome after complicated minor head injury. *AJNR Am J Neuroradiol.* Mar 2008;29(3):506-513.
202. Whitmore RG, Thawani JP, Grady MS, Levine JM, Sanborn MR, Stein SC. Is aggressive treatment of traumatic brain injury cost-effective? *Journal of neurosurgery.* May 2012;116(5):1106-1113.
203. Faul M, Wald MM, Rutland-Brown W, Sullivent EE, Sattin RW. Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: testing theBrain Trauma Foundation guidelines for the treatment of severe traumatic brain injury. *The Journal of trauma.* Dec 2007;63(6):1271-1278.
204. Center for Medicare & Medicaid Services. CMS files for download for Medicare payment systems. 2013 physician fee schedule payment file national/carrier. http://www.cms.gov/apps/physician-fee-schedule/overview.aspx. Accessed July 10, 2013.
205. Patwardhan RV, Nanda A. Implanted ventricular shunts in the United States: the billion-dollar-a-year cost of hydrocephalus treatment. *Neurosurgery.* 2005;56(1):139-144; discussion 144-135.
206. American Health Care Association. *2012 Report on Shortfalls in Medicaid Funding for Nursing Home Care* http://www.ahcancal.org/research_data/funding/Pages/2012-Medicaid-Shortfall-Report.aspx. Accessed July 10, 2013.
207. Traumatic Brain Injury Model Systems National Database. 2014. http://www.tbindsc.org.
208. US Department of Labor. Bureau of Labor Statistics. Consumer Price Indexes. http://www.bls.gov/cpi/ - data. Accessed July 10, 2013.
209. Gold MR. *Cost-Effectivness in Health and Medicine.* New York, NY: Oxford University Press; 1996.
210. Naimark DM, Kabboul NN, Krahn MD. The half-cycle correction revisited: redemption of a kludge. *Medical decision making : an international journal of the Society for Medical Decision Making.* Oct 2013;33(7):961-970.
211. Owens DK. Interpretation of cost-effectiveness analyses. *Journal of general internal medicine.* Oct 1998;13(10):716-717.

212. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical decision making : an international journal of the Society for Medical Decision Making.* Jul-Aug 2002;22(4):290-308.
213. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation.* Oxford, UK: Oxford University Press; 2006.
214. Koerkamp BG, Weinstein MC, Stijnen T, Heijenbrok-Kal MH, Hunink MGM. Uncertainty and Patient Heterogeneity in Medical Decision Models. *Med Decis Making.* Mar-Apr 2010;30(2):194-205.
215. Quinn RR, Naimark DM, Oliver MJ, Bayoumi AM. Should hemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* Sep 2007;50(3):421-432.
216. Ho KM, Honeybul S, Lind CR, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *The Journal of trauma.* Dec 2011;71(6):1637-1644; discussion 1644.
217. Hammond FM, Grattan KD, Sasser H, et al. Five years after traumatic brain injury: a study of individual outcomes and predictors of change in function. *NeuroRehabilitation.* 2004;19(1):25-35.
218. Faul M, Wald MM, Xu L, Coronado VG. *Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002-2006.* Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
219. Richard I, Hamon M, Ferrapie A, Rome J, Brunel P, Mathe J. Tracheotomy in brain injured patients: which patients? Why? When? How? *Ann Fr Anesth Reanim.* Jun 2005;24(6):659-662.
220. Gurkin SA, Parikshak M, Kralovich KA, Horst HM, Agarwal V, Payne N. Indicators for tracheostomy in patients with traumatic brain injury. *The American surgeon.* Apr 2002;68(4):324-328; discussion 328-329.
221. Keren O, Cohen M, Lazar-Zweker I, Groswasser Z. Tracheotomy in severe TBI patients: sequelae and relation to vocational outcome. *Brain injury : [BI].* Jun 2001;15(6):531-536.
222. Klingbeil GE. Airway problems in patients with traumatic brain injury. *Archives of physical medicine and rehabilitation.* Jul 1988;69(7):493-495.
223. Lajtman Z, Gasparovic S. Prognostic value of Glasgow Coma Scale for tracheotomy in head injured patients. *Acta medica Croatica : casopis Hravatske akademije medicinskih znanosti.* 1996;50(3):133-136.
224. Nieszkowska A, Combes A, Luyt CE, et al. Impact of tracheotomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients. *Critical care medicine.* Nov 2005;33(11):2527-2533.
225. Moller MG, Slaikeu JD, Bonelli P, Davis AT, Hoogeboom JE, Bonnell BW. Early tracheostomy versus late tracheostomy in the surgical intensive care unit. *American journal of surgery.* Mar 2005;189(3):293-296.

226. Frank JA, Matthay MA. Science review: mechanisms of ventilator-induced injury. *Crit Care.* Jun 2003;7(3):233-241.
227. Gomes Silva BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev.* 2012;3:CD007271.
228. National Trauma Data Bank. National Trauma Data Standard Data Dictionary, 2011 Admissions. http://www.ntdsdictionary.org/dataElements/datasetDictionary.html. Accessed December 21, 2011.
229. Sturmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *Journal of clinical epidemiology.* May 2006;59(5):437-447.
230. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *American journal of epidemiology.* Aug 1 2003;158(3):280-287.
231. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Statistics in medicine.* Jun 30 2006;25(12):2084-2106.
232. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *The Journal of thoracic and cardiovascular surgery.* Nov 2007;134(5):1128-1135.
233. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. *Proceedings of the Twenty-sixth Annual SAS Users Group International Conference.* 2001;26:214-226.
234. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharmaceutical statistics.* Mar-Apr 2011;10(2):150-161.
235. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research.* May 2011;46(3):399-424.
236. Austin P, Rothwell D, Tu J. A comparison of statistical modeling strategies for analyzing length of stay after CABG surgery. *Health Serv Outcomes Res Methodol.* 2002;3(2):107-133.
237. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ.* 2010;340:b5087.
238. Mantel N, Byar DP. Evaluation of response-time data involving transient states - illustration using heart-transplant data. *J Am Stat Assoc.* 1974;69(345):81-86.

239. Scales DC, Thiruchelvam D, Kiss A, Redelmeier DA. The effect of tracheostomy timing during critical illness on long-term survival. *Critical care medicine.* Sep 2008;36(9):2547-2557.
240. Suissa S. Immortal time bias in pharmaco-epidemiology. *American journal of epidemiology.* Feb 15 2008;167(4):492-499.
241. Lee EW, Wei LJ, Amato DA. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein J, Goel P, eds. *Survival Analysis: State of the Art*: Springer; 1992:237–245.
242. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics.* Sep 1998;54(3):948-963.
243. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. *The New England journal of medicine.* Apr 19 2012;366(16):1467-1476.
244. Heffner JE, Miller KS, Sahn SA. Tracheostomy in the intensive care unit. Part 1: Indications, technique, management. *Chest.* Aug 1986;90(2):269-274.
245. MacIntyre NR, Cook DJ, Ely EW, Jr, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest.* Dec 2001;120(6 Suppl):375S-395S.
246. Heffner JE, Hess D. Tracheostomy management in the chronically ventilated patient. *Clinics in chest medicine.* Mar 2001;22(1):55-69.
247. Bours GJ, De Laat E, Halfens RJ, Lubbers M. Prevalence, risk factors and prevention of pressure ulcers in Dutch intensive care units. Results of a cross-sectional survey. *Intensive care medicine.* Oct 2001;27(10):1599-1605.
248. Patel R, Cook DJ, Meade MO, et al. Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *Journal of critical care.* Dec 2005;20(4):341-347.
249. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet.* Jan 19 2002;359(9302):248-252.
250. Jiang JY, Xu W, Li WP, et al. Efficacy of standard trauma craniectomy for refractory intracranial hypertension with severe traumatic brain injury: a multicenter, prospective, randomized controlled study. *J Neurotrauma.* Jun 2005;22(6):623-628.
251. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. *Neurosurgery.* Nov 2001;49(5):1166-1184; discussion 1184-1166.
252. Stein SC, Burnett MG, Sonnad SS. Shunts in normal-pressure hydrocephalus: do we place too many or too few? *Journal of neurosurgery.* Dec 2006;105(6):815-822.
253. Kulkarni AV, Drake JM, Rabin D, Dirks PB, Humphreys RP, Rutka JT. Measuring the health status of children with hydrocephalus by using a new outcome measure. *Journal of neurosurgery.* Nov 2004;101(2 Suppl):141-146.
254. Drake JM, Kulkarni AV, Kestle J. Endoscopic third ventriculostomy versus ventriculoperitoneal shunt in pediatric patients: a decision analysis. *Child's*

nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery. Apr 2009;25(4):467-472.

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Parts of Chapters 2, 3 and 4 were reprinted from:

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