The Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Traumatic Brain Injury : A Systematic Review and Meta-Analysis

Mémoire

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Sous la direction de :

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Résumé

Les traumatismes craniocérébraux constituent une cause importante de mortalité et de morbidité à travers le monde, et représentent un fardeau socioéconomique important dans les pays développés en raison de l'incapacité résiduelle post-traumatique dont souffrent les patients après leur traumatisme. Malgré la fréquence élevée d'issues cliniques défavorables à long terme, il existe actuellement peu d'indicateurs pronostiques permettant de guider le clinicien dans la prise en charge aiguë de ces patients et de conseiller leurs familles et proches. Plus de quatre décennies d'études observationnelles ont examiné l'utilisation de l'imagerie par résonance magnétique effectuée en phase aiguë dans son rôle potentiel à distinguer rapidement l'issue clinique post-traumatisme à long terme chez ces patients. Le présent travail vise donc à déterminer la valeur pronostique de l'imagerie par résonance magnétique effectuée en phase aiguë de traitement suite à un traumatisme craniocérébral modéré ou grave chez l'adulte, en utilisant une méthodologie de revue systématique et méta-analyse pronostique, afin d'identifier toutes les études évaluant la relation entre les modèles de lésions identifiés par résonance magnétique et l'issue clinique à long terme.

Nos travaux ont identifié 58 études individuelles. Après méta-analyse, les lésions localisées dans le tronc cérébral se sont révélées être associées à une mortalité augmentée (toutes causes confondues) et une issue neurologique défavorable alors que les lésions compatibles avec une lésion axonale diffuse ont été associées à une augmentation du risque d'issue neurologique défavorable. Deux échelles de classement basées sur la gravité de la lésion ont été associées à des issues neurologiques de plus en plus défavorables au fur et à mesure de l'augmentation du nombre de structures cérébrales caudales touchées, confirmant ainsi l'importance des lésions profondes. Ces résultats démontrent l'utilité pronostique de l'imagerie par résonance magnétique effectuée rapidement après un traumatisme craniocérébral et indiquent la nécessité d'entreprendre des études pronostiques de cohorte de haute qualité et bien contrôlées, en raison du risque élevé de biais dans la littérature actuelle.

Abstract

Traumatic brain injury is a major cause of mortality and morbidity worldwide and represents a significant socioeconomic burden in developed nations due to residual post-trauma disability among survivors. Despite high rates of long-term unfavourable outcome, few prognostic indicators currently exist to guide early clinical management and counsel family and friends of patients. Over four decades of observational studies have examined the potential role of early magnetic resonance imaging of the brain to distinguish long-term clinical outcome by examining lesion patterns identifiable soon after trauma. This present work thus aims to determine the prognostic value of early magnetic resonance imaging following moderate or severe traumatic brain injury in adults by employing prognostic systematic review and meta-analysis methodology to identify all published studies assessing the relationship between magnetic resonance lesion patterns and long-term clinical outcome.

Our search identified 58 individual studies; following meta-analysis, lesions located in the brainstem were associated with all-cause mortality and unfavourable neurological outcome while shear injury patterns compatible with diffuse axonal injury anywhere in the brain were associated with increased risk of unfavourable neurological outcome. Two scoring systems based on lesion depth were associated with progressively worse neurological outcomes as more caudal cerebral structures were affected, confirming the importance of deep lesions. These findings demonstrate the prognostic utility of magnetic resonance imaging early following traumatic brain injury and indicate the need for high quality, well-controlled, prognostic cohort studies given the elevated risk of bias in the current body of literature.

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List of Abbreviations and Acronyms

BAEP	brainstem auditory evoked potential
BI	Barthel index
CHART	Craig Handicap Assessment and Reporting Technique
CHU	*Centre Hospitalier Universitaire*
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CT	computed tomography
DAI	diffuse axonal injury
DRS	Disability Rating Scale
EDH	epidural hematoma
EEG	electroencephalogram
FLAIR	fluid-attenuated inversion recovery
FRQS	Fonds de Recherche du Québec—Santé
GOS	Glasgow Outcome Scale
GOSe	extended Glasgow Outcome Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	intensive care unit
IMPACT	International Mission for Prognosis and Analysis of Clinical Trials in TBI
MeSH	Medical Subject Heading
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NINDS	National Institute of Neurological Disorders and Stroke
NSE	neuron specific enolase
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROGRESS	Prognosis Research Strategy
PROSPERO	Prospective Register of Systematic Reviews
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
QUIPS	Quality in Prognostic Studies
RCT	randomized controlled trial
RR	risk ratio
SSEP	somatosensory evoked potential
STROBE	Strengthening of Reporting of Observational Studies
SWI	susceptibility weighted imaging
T	Tesla
T1WI	T1-weighted imaging
T2WI	T2-weighted imaging
T2*-GRE	T2*-gradient echo
TBI	traumatic brain injury
tSAH	traumatic subarachnoid hemorrhage
WLST	withdrawal of life-sustaining therapy

This thesis is dedicated to the innumerable people who inspire and support me to be a better physician and scientist.

Wer fertig ist, dem ist nichts recht zu machen,
Ein Werdender wird immer dankbar sein.
Johann Wolfgang von Goethe, *Faust*, 1808

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My sincere thanks also go to the extraordinary research team with whom I worked and learned from on a near daily basis at the Traumatology-Emergency-Critical Care Medicine research unit at the CHU de Québec-Université Laval and the Canada Research Chair in Critical Care Neurology and Trauma. In particular, I extend my thanks to Amélie Boutin, Michèle Shemilt, Caroline Leclerc, and Olivier Costerousse who provided direct and continued support at the ground level, who served as examples of experienced epidemiologists, and who provided daily direction during the undertaking of my research, especially in the early phases. I furthermore express my immense gratitude to my remaining co-authors: Mathieu Laflamme, François Lauzier, Lynne Moore, Ryan Zarychanski, Vincent Douville, and Dean Fergusson – all of whom similarly provided extensive feedback and direction in structuring, writing, and revising what would become my first scholarly publications and the core content of this thesis.

In addition to my colleagues, I am immensely fortunate to have had the close support of my family and friends accompanying me on this journey. In particular, I thank both my parents for embodying the such impressive examples as academics and scientists, nurturing my interest in medicine for as long as I can remember. I thank especially my mother, Shahrzad Saif, whose indispensable support and encouragement throughout the process ensured the eventual successful completion of this thesis and to whom I am eternally

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Preface

This master's thesis comprises the design and completion of a prognostic factor systematic review and meta-analysis undertaken under the supervision of Alexis Turgeon (Canada Research Chair in Critical Care Neurology and Trauma).

Resulting from this study, two separate research manuscripts form the body of the thesis, both of which have been published as articles in peer-reviewed medical journals. The first article, entitled "The Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis Protocol" comprises the *a priori* designed study protocol for the planned systematic review which was published in *Systematic Reviews* in 2016 and is incorporated in full and unchanged as Chapter 1 in this thesis.[1] The second article, entitled "The Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis" comprises the report of the results of the full systematic review and meta-analysis which was published in *Critical Care Medicine* in 2017 and is incorporated in full and unchanged as Chapter 2 in this thesis.[2]

The first author of both of these articles is also the author of this thesis. As first author, I designed the study protocol, wrote and prepared the protocol for publication, created the systematic search strategy, identified eligible studies, extracted study data, undertook data analysis, designed and created tables and figures, and wrote and prepared the study manuscript for publication. Alexis Turgeon designed the study question and provided direct supervision at all stages of the study and during the production of both manuscripts for publication, acting as senior and corresponding author in the publication process. Co-authors François Lauzier, Lynne Moore, Ryan Zarychanski, Amélie Boutin, Michèle Shemilt, and Dean Fergusson have also made substantial contributions to the conception and design of this study. Co-authors Mathieu Laflamme and Vincent Douville also contributed to identifying eligible studies and extracting study data. All authors critically revised both manuscripts for important intellectual content prior to publication.

Introduction

General Introduction

In reviewing the scientific literature to identify the existing foundation of evidence which underlies the clinical outcomes and prognostic assessment of patients suffering moderate or severe traumatic brain injury (TBI), this introductory chapter serves to situate existing prognostic indicators of TBI in the epidemiological context of the disease, describe the application of magnetic resonance imaging (MRI) in this condition as well as other neurological emergencies, and propose methodological strategies for conducting a systematic review and meta-analysis to rigorously determine the predictive value of lesions found on brain MRI performed in the acute phase of care for long-term outcomes in moderate or severe TBI.

We begin by defining and classifying TBI, along with a discussion of its epidemiology and socioeconomic impact on both a local and global scale, then continue on to review the injury sub-types, management considerations, and overall prognosis seen in contemporary patients with TBI, with a subsequent assessment of established clinical and paraclinical prognostic indicators frequently employed to predict outcome in this population. This is followed by an introduction to MRI physics, imaging sequences, and their applications to neuroanatomy, with particular emphasis on the utility of MRI in TBI and its overall superiority as compared with computed tomography (CT). Consideration is given to feasibility of MRI in the acute phase of critical illness, along with the practical limitations of this modality in patients with moderate or severe TBI, and examples where this modality is successfully employed in the acute phase of neurological emergencies. Lastly, the methodology for the conduct of a prognostic factor systematic review and meta-analysis is reviewed, describing the specific tools designed and validated for this relatively novel form of systematic review. We end by describing the objectives which underlie the design of our prognostic factor systematic review, targeting the quantitative synthesis of prognostic observational cohort studies assessing the association of lesions identified on MRI with long-term mortality and neurological outcomes in patients with moderate or severe TBI.

Traumatic Brain Injury

Definition

Traumatic brain injury represents a spectrum of cerebral lesions and clinical presentations culminating from trauma inflicted to the head; it has been therefore defined by the National Institute of Neurological Disorders and Stroke (NINDS) as an alteration in the brain's function, or the evidence of brain pathology, induced by an external force.[3] Compared with the narrower Word Health Organization[4] or American Congress of Rehabilitation Medicine[5] definitions, the breadth of interpretation permitted by these three criteria employed in the NINDS definition more adequately acknowledges the overall heterogeneity of TBI as a diagnosis, and the need for any

single definition to reflect the wide range of clinical presentations which may arise as a result of trauma to the head.[6]

As an acquired condition secondary to external mechanical force, the underlying mechanisms leading to head trauma frequently differ between cases and may be grossly categorized as either penetrating trauma, where there is open communication between the brain (or other intracranial structures) and the exterior environment occurring due to the traumatic insult, or as blunt trauma, where the injury is caused by an external impact whose transfer of force to the closed cranial vault causes damage to internal cerebral structures.[7,8]

Similarly, just as the aetiology of trauma may differ, the downstream effect of the external impact on the brain may be very variable within these two subtypes of head injury or may even vary between two patients with the same mechanism of trauma. The clinical manifestations of what is defined as alteration in the brain's function may therefore be very broad, but frequently consists of: a period of loss of consciousness, temporary or permanent post-traumatic amnesia, and the new onset of focal neurological deficits (such as motor weakness, loss of sensation, impairment of speech, or impairment of vision).[3,6,7]

The ability to demonstrate the presence or absence of brain pathology (as well as determine its significance on long-term outcome) is a function of both the mechanism and intensity of the traumatic force received and the sensitivity of the imaging modalities and clinical or paraclinical tests employed for its detection. While the former topic is discussed in greater detail in a subsequent section (*Pathophysiology, Injury Sub-Types, and Implications for Management*), the discussion of the diagnostic and prognostic yield of neuroimaging in TBI is a major objective of our research, forming the leading question of our study, and will be addressed in detail throughout the course of this thesis.

Epidemiology

Traumatic brain injury is a major global health problem and is the leading cause of death among individuals under the age of 45 in North America.[9] Worldwide, more than 50 million TBIs are estimated to occur annually;[7] mild TBI accounts for 55% of all cases, with moderate and severe TBI representing 27.7% and 17.3% of cases, respectively.[10] In the United States alone, upwards of 3.5 million cases of TBI occur annually[11] and, among those with moderate or severe TBI, nearly half who survive the acute period post-trauma will go on to suffer significant long-term disability with neurological or functional impairment.[12,13] This prevalence has been estimated at 3.2 to 5.3 million individuals, representing more than 2% of the United States' population.[14–16]

In adult populations, moderate and severe TBI has a bimodal age distribution, with the highest rates occurring in either young adults aged between 15-24 years or older adults aged >75 years.[17] In the latest report on vital statistics by the Centre for Disease Control in the United States, the most common mechanisms for

injury were identified to be falls, being struck by an object, and motor vehicle collisions;[17] while TBI-related hospital admissions for motor vehicle collisions were noted to be on the decline, there has been a concomitant increase in admissions due to falls in older adults, driving an increase in the overall rate of hospitalizations for TBI.[17] Apart from age, sex is a risk factor for TBI, with males at higher risk than females.[17] Further risk factors include lower socioeconomic status, substance use disorder, and a history of psychiatric or cognitive comorbidity.[18,19]

The incidence of TBI varies widely internationally, ranging from the lowest rates seen in Western Europe at 7.3 per 100 000/year, to the highest observed in Asia and New Zealand (the latter at 811 per 100 000/year).[7,10,20] While motor vehicle collisions are the leading cause of TBI in low- and middle-income countries, falls are increasingly responsible for most cases of TBI in developed nations.[7,10] In Ontario, Canada, 227 605 individuals suffered TBI in 2010, with over 40% of them aged between 18-39 years.[21] The age- and sex-adjusted incidence of TBI was determined to have increased from 130 per 100 000/year to 170 per 100 000/year over the course of seven years from 2004 to 2011.[21] In Québec, Canada, recent data published in 2019 from the Institut d'Excellence en Santé et Services Sociaux (INESSS) reporting hospitalizations for TBI in the province of Québec demonstrated that 6 089 patients were admitted for moderate or severe TBI between 2013-2016.[22] Although representing only 11.7% of all trauma admissions in that time period, patients with moderate or severe TBI had a disproportionately high mortality rates: 18.2% of this population died during hospitalization compared to the 5.1% morality rate seen in the general trauma population.[22] Further, while an annual decrease in the number of cases of moderate TBI was noted in this timeframe, a concomitant increase in the rates of severe TBI was also observed.[22]

Socioeconomic Impact

The socioeconomic implications of TBI are vast and attributable to a combination of elevated acute health-care resource expenditure related to the index hospitalization, chronic complex care requirements due to significant long-term disability, and loss of productivity given the high incidence of this condition in otherwise young individuals. As the majority of moderate or severe TBI occurs in individuals who were otherwise in good health without comorbidity,[23] the magnitude of indirect costs of this condition are considerable, resulting in a massive loss of productivity from the workforce due to both the patients' disabilities and the added potential necessity for familial caregivers. Survivors of moderate or severe TBI may experience an undue burden of physical, mental, and cognitive disabilities which persist long-term after the index trauma and these may result in complex care needs and social supports not readily apparent in the acute phase of trauma.[7]

The economic impact of TBI in the United States alone was estimated at over $76.5 billion in 2010 when both direct and indirect costs were considered, up from $60.4 billion in 2000.[24,25] In Ontario, the mean direct cost of healthcare expenditure per patient in the first year (incident year) following TBI has been estimated

at $9 277, and subsequently $3 854/year thereafter (prevalent years) for each case of TBI.[21] This expenditure increases with patient age, reaching an approximate nadir of over $27 000/year for patients above 65 years, with over 40% of these costs attributable to hospitalizations alone.[21] In patients with severe TBI, the incident year expenditures are much higher, at $32 132/year, representing the need for critical care and specialist intervention in this population.[26] Overall total medical costs for the first year of new cases of severe TBI in Ontario are therefore estimated at $120.7 million for incident cases in this province alone.[26]

Classification of Severity

TBI is most commonly classified according to its clinical severity as assessed by the Glasgow Coma Scale (GCS). This 15-point scoring system initially developed in 1974[27] is widely used internationally for assessing the depth of unresponsiveness as a measure of coma. At the time of first medical contact, the patient's responsiveness is graded over three different domains of reaction to stimuli (eye, verbal, and motor) and the score is summed to produce a total score of 3 to 15. In TBI, patients are then classified into groups of GCS 3-8 (severe TBI), GCS 9-12 (moderate TBI), and GCS 13-15 (mild TBI).[27]

While the GCS remains the main method employed for grading severity in TBI due to its simplicity of use in the field or at bedside coupled to its high degree of reproducibility,[7] alternative clinical models have also been proposed. The United States Department of Defense and Department of Veterans Affairs, for example, employs an assessment of duration of post-traumatic amnesia and duration of post-trauma loss of consciousness, in addition to GCS, to further refine the assessment of TBI severity.[28] Neuroimaging findings, in particular via computed tomography (CT), have also been proposed as a method of classifying patients into categories of severity based on neuroradiological findings such as signs of swelling, focal lesions, hemorrhage, skull fracture and/or lesion localisation.[29–31] However, as this implies delaying the assessment of severity until imaging is acquired and does not integrate the patient's clinical status, it is best considered as an additional assessment of severity when an initial appreciation of the patient's condition has already been established via the GCS.

Pathophysiology, Injury Sub-Types, and Implications for Management

While a heterogeneous process, the underlying pathophysiology of the injury suffered by the brain following TBI can be conceptualized as two separate, but closely interrelated, processes typically described as primary brain injury, occurring at the time of trauma, and secondary brain injury, occurring over the hours to days following the initial trauma.[6]

Primary brain injury is the insult that occurs at the time of trauma; although itself heterogeneous in origin, it arises from whatever environmental mechanism was responsible for transferring external force to intracranial contents, and thus inducing direct damage to the brain.[6] Primary brain injury can be further

conceptualized as either focal or diffuse and intra-axial (within the brain parenchyma) or extra-axial (within the skull but outside of the brain itself). Variations in mechanism of injury may tend to favour the production of certain lesion phenotypes, although there is considerable overlap and multiple types of lesions frequently coexist in the same patient. Mechanisms of direct impact, such as falls, favour the development of focal lesions such as extra-axial hematomas or focal cerebral contusions, while cases of rapid acceleration and deceleration, such as those occurring following motor vehicle collisions, may favour the development of diffuse shear injuries consistent with diffuse axonal injury (DAI) or multi-focal cerebral contusions associated with coup-contrecoup injury.[8,32–34] Different lesions carry vastly different prognoses; while focal extra-axial lesions such as epidural and subdural hematomas may be amenable to surgical evacuation, diffuse shear injury such as that seen in suspected cases of DAI has been associated with extended periods of coma, poor neurological outcomes, and high rates of long-term mortality.[35,36]

Secondary brain injury is a broad term grouping the array of physiological or pathophysiological host responses to brain trauma.[6,37] These are hypothesized to be mediated by a cascade of processes, including molecular injury mechanisms, sympathetic hyperreactivity, autoimmune cross-reactivity, and coagulopathy.[37–43] Experimental models have demonstrated the variable occurrence of microvascular occlusion, vasospasm, activation of apoptotic pathways, mitochondrial dysfunction, or neurotransmitter induced excitotoxicity all leading to the downstream effect of further neuronal cell death, cerebral oedema, and elevations in intracranial pressure which maintain and exacerbate injury to the brain.[37,44–47]

The anticipation and identification of both primary and secondary brain injuries should begin from the time of first contact with medical care and is vital as management strategies for patients with moderate or severe TBI centre on the targeted treatment of both types of brain injury. In the acute phase of hospital care following TBI, critical supportive and surgical measures may immediately target the manifestations of primary brain injury, such as the drainage of extra-axial hematomas, the placement of an interventricular drain, or, occasionally, decompressive craniectomy.[7,48] Simultaneously, the anticipation, prevention, and/or treatment of secondary brain injury should also be routinely conducted; while no clinical trials in humans have demonstrated the benefit of any targeted treatments of secondary injury pathways, supportive management may prevent or mitigate the extent of secondary brain injury post-TBI.[7,48] This includes active intensive monitoring for the avoidance of hypotension or hypoxia,[49,50] the rapid identification and treatment of seizures, and the control of intracranial pressure to maintain safe cerebral perfusion pressures.[7,48] The latter potentially requires additional measures of sedation, hyperosmotic infusions, or the optimization of mechanical ventilation to avoid hypercapnic cerebral vasodilation.[7,48] While controversial due to conflicting evidence,[7] the latest Brain Trauma Foundation guidelines for the management of severe TBI still emphasize the use of goal-directed therapy for the prevention and

mitigation of secondary brain injury and thus describe homeostatic thresholds for systolic blood pressure, intracranial pressure, and cerebral perfusion pressure.[48]

Long-Term Prognosis

Patients with moderate or severe TBI are typically critically ill with high rates of mortality early in their clinical course; increasing levels of TBI severity are consistently associated with decreased survival. A systematic review analyzing survival in severe TBI over the past 150 years demonstrated a more than 50% historic decrease in mortality in this population, likely associated with improvements in medical and surgical management, which has since stagnated and remained largely unchanged over the past quarter century.[51] Contemporaneous observational cohort studies indicate a case-fatality rate now reaching upwards of 35% in patients with severe TBI.[51] This is likely highly age-dependent as a meta-analysis of 24 studies pooling data on elderly patients ≥60 years old found an in-hospital mortality rate of 57% and a 6-month mortality rate of 75% in this population.[52] While up to 15% of patients with severe TBI are discharged from their index hospitalization in a vegetative state,[53–55] significant proportions of cases (30-65% of all severe TBI overall) do eventually attain independent function following prolonged periods of convalescence.[13,56–58] In those discharged in a vegetative state specifically, however, only half go on to recover consciousness at one year and effectively all remain totally dependent long-term for external care due to severe functional disability.[53–55]

Although survival is an important outcome in moderate and severe TBI, there are limitations inherent to this metric which must been considered when interpreting it as a clinical endpoint in this population. Frequently, death in critically ill patients having suffered moderate or severe TBI occurs following a decision to withdraw life-sustaining therapies.[59] As such patients often lack the capacity to make medical decisions in the acute phase following the trauma, the decision to implement, continue, or withdraw life-sustaining treatments depends on the judgment of patient families and medical teams seeking to best balance patients' preferences for treatment with an estimation of the potential for meaningful neurological recovery if intensive life-sustaining therapies are pursued. Despite few robust prognostic factors in the early phase following TBI, over half of such decisions to withdraw life-sustaining therapies are made within the first three days of admission.[59] These decisions, and the resultant effect on mortality statistics, may thus be influenced by the treating physicians' subjective impressions of prognosis and past experiences with similar cases and therefore frequently vary from one treating team to another.[60,61] As a consequence of this, a multicentre cohort study on this subject found considerable variability in mortality rates for moderate and severe TBI between centres in Canada, with the primary driver demonstrated to be differences in the incidence of withdrawal of life-sustaining therapy.[59]

In contrast to mortality, long-term functional outcomes are likely more clinically relevant to patients and family members considering the important burden associated with the injury. Long-term functional status following TBI may be assessed with the use of standardized clinical scales; the standard[62] and extended[63]

Glasgow Outcome Scales (GOS and GOSe, respectively) are arguably the best validated and most widely used outcome scores in patients with TBI given the extensive historical experience in their use and their high interrater reliability.[64] The GOS establishes five stages of function ranging from death (stage 1) to absent or minimal impairment (stage 5), with vegetative state at stage 2 and stages 3 and 4 as severe and moderate functional impairments, respectively.[62] The GOSe divides stages 3, 4, and 5 each into two separate categories of intermediary function, which has been demonstrated to improve discrimination is generally now the recommended version of the scale.[63,64] Frequently, scores are further dichotomized into GOS stages 1 to 3 and GOSe stages 1 to 4 as representing unfavourable neurological outcome and GOS stages 4 to 5 and GOSe stages 5-8 representing favourable neurological outcome.

Established Prognostic Indicators for Traumatic Brain Injury

In the existing literature on TBI, the search for reliable prognostic indicators spans a diverse range of factors including demographic and clinical factors, electrophysiological monitoring parameters, laboratory parameters, biomarkers and neuroimaging findings, including CT and MRI.[7,53,65] The most robust evidence to date on prognostic indicators on admission in TBI comes from the IMPACT database,[65] which combines data from eight randomized controlled trials and three observational trials in TBI; this merger permits extensive prognostic analyses with high statistical power. Based on the IMPACT database, univariable analyses have identified a number of factors measurable during the acute phase of hospitalization which correlate with GOS at 6 months. Multivariable analyses have further narrowed this list to a select handful of factors that may be confidently established as independent prognostic indicators.

Such multivariable analyses from the IMPACT study have determined concretely that age, pupillary response to light, and the motor subscale of the GCS are the three most powerful independent predictors of outcome in acute TBI.[65] Age in particular was found to be the most powerful predictor among all the factors studied, with the prognostic value of several other factors, such as injury mechanism, in univariable analyses being themselves dependant primarily on age.[65]

Two specific laboratory parameters have been found to have strong correlation with GOS at 6 months. The first being prothrombin time which, in multivariable analyses, maintain a predictive value comparable to that of pupillary reactivity and CT findings in fully adjusted models, likely the reflection of the importance of coagulopathy in this population.[65] Glucose was also identified as a strong independent prognosticator on multivariable analysis;[65] this is of significant interest as there has been considerable research in the possible neurotoxic effects of presenting and persistent hyperglycaemia post-trauma in general and the role of glucose in secondary brain injury after TBI.[66] The use of intensive insulin therapy in critically ill patients to maintain strict normoglycaemia has been the subject of significant study in the greater critical care population[67–69] and it remains controversial in TBI patients.[70] The identification of these two commonly requested laboratory tests as being

predictive of outcome is valuable as they are ubiquitous, as well as simple to demand and interpret, in the acute phase of care.

In the IMPACT study, the most prognostically-important lesion patterns on acute CT scans were found to be the Marshall CT classification[30] and the presence of traumatic subarachnoid haemorrhage (tSAH).[65] Globally, the Marshall classification is a CT estimation of total lesion burden and mass effect following TBI, graded in increasing severity.[30] Even following multivariable analysis, the Marshall classification was found to retain relatively significant associations with long-term outcome. Given the near universal acquisition of CT imaging in TBI patients at the time of their presentation to hospital, this simple CT classification may therefore permit early prognostication at the time of hospital admission. Presence of tSAH on initial CT is also a useful finding, with a strong correlation with poor outcome on fully adjusted models when present.[65] Interestingly, the presence of epidural hematoma on CT was associated with a favourable long-term prognosis in multivariable analysis.[65] This possibly reflects the generally good response of epidural hematoma (EDH) to rapid surgical evacuation; if EDH is the sole manifestation of head trauma, it is reasonable to assume this select population of patients will have more favourable outcome than average TBI patients who may have a more complex combination of diffuse and local cerebral lesions.

Several other modalities have been assessed as potential prognostic indicators. While possibly useful for acute monitoring, conventional electroencephalography (EEG) itself has been found to have limited independent prognostic potential, possibly due to its susceptibility to interference from anaesthetics and other drugs commonly used for sedation in the acute phase post-TBI;[71] quantitative EEG is an alternative modality which is under investigation as an emerging electrophysiological prognostic tool.[72] Other electrophysiological parameters have been found to have potential prognostic applications in TBI: abnormal brainstem auditory evoked potentials (BAEPs) correlate with unfavourable outcome while normal BAEPs do not seem to carry any predictive value.[73] Somatosensory evoked potentials (SSEPs) however, may have more robust prognostic applications in TBI.[74,75] A review of acute severe TBI patients found that presence of normal SSEPs had a positive predictive value (PPV) of 71.2% for favourable GOS, while absence of SSEPs bilaterally had a PPV of 98.5% for unfavourable GOS.[74,76] Head-to-head comparison studies between BAEP and SSEP have further confirmed the superiority of SSEP over BAEP.[77–80] Researchers in this domain have found that better results in prediction are obtained if these measures are attained promptly, highlighting the importance of early acute phase application of these methods.[78,81]

Several novel serum biomarkers have been under investigation for their potential predictive value post-TBI. Among these, the S-100β protein is arguably the most studied and most promising; a recent meta-analysis encompassing 41 studies (2 RCTs and 39 cohort studies) found a significant positive association between serum concentrations of S-100β protein post-TBI and mortality and unfavourable long-term GOS with a proposed cut-

off definition maximizing specificity.[82] Neuron-specific enolase is another emerging biomarker with potential to act as an early prognosticator following TBI; a meta-analysis of 30 cohort studies found significant positive associations between neuron-specific enolase levels and both mortality and unfavourable long-term GOS.[83] Lastly, serum levels of glial fibrillary acidic protein following moderate and severe TBI has also been shown to have significant associations with mortality and GOS in a meta-analysis of 10 cohort studies.[84] However, in the case of the latter two biomarkers, existing patient data does not permit the establishment of clear thresholds. While encouraging, clinical use of these proteins remains of uncertain utility as optimal threshold values and sampling times post-trauma have not been clearly determined; their application in future studies investigating their multimodal combination with other prognosticators for outcome prediction may permit the development of more refined risk prediction tools.[82–84]

Magnetic Resonance Imaging

Introduction and Magnetic Resonance Physics

Magnetic resonance imaging (MRI) technology provides detailed assessment of anatomy and physiology via the indirect imaging of protons, particles abundant in the human body within hydrogen atoms.[85,86] MRI scanners produce a static magnetic field with a defined directional vector; when a patient is placed within this field, each individual hydrogen proton acts as its own magnet and spins to either align with or oppose to the overall field.[85,86] The summation of each proton's spin can be employed to compute an overall net magnetization vector, and this can be situated in a three-dimensional plane, defined by the three orthogonal directions *x*, *y*, and *z*. Three corresponding orthogonal sets of gradient coils are set, and any slight alteration in the overall strength of the magnetic field as a result of radiofrequency pulses may be detected.[85,86] To generate an MRI image of a structure, such as the brain, radiofrequency pulses are used to excite the protons' magnetic spins of interest, bringing them to a higher energy state, and moving the net magnetization vector away from the overall direction of the MRI scanner's magnetic field.[85,86] The degree to which this movement occurs defines a "flip angle", and this is directly correlated to the amount of energy deposition in the tissue under study and the strength and duration of the radiofrequency pulse (which is standardized for each sequence protocol).[85,86] The strength of the magnetic field is expressed in the units Tesla (T) and is generated by a superconducting cylindrical bore magnet; in most clinical systems, a field strength of either 1.5 T or 3.0 T is generated and this field strength defines both the imaging speed and resolution.[86]

In generating spin echo pulse sequences, a 90-degree radiofrequency pulse is administered to excite the tissue under study followed by a 180-degree refocusing pulse.[85] Electromagnetic energy absorbed by tissue is then released by several mechanisms simultaneously. The first, longitudinal magnetisation recovery, is represented by the time constant T1, defined as the time it takes for the longitudinal component of the magnetization vector to return to 63% of its original state.[85,86] T1 is a physical characteristic of the tissues under

study and is also affected by the strength of the scanner's field.[85] In T1-weighted imaging (T1WI) sequences, the time between delivery of two flip angles is kept short, and images are therefore generated which demonstrate the spectrum of differences in T1 between the different tissue types under study, generating the radiological image.[85,86]

The second, transverse magnetization decay, is a product of the interactions between the neighbouring spins of two protons; this causes a loss of the transverse component of the net magnetization vector.[85,86] This exponential loss is typically defined by the time constant T2, which like T1 is tissue-specific but is less dependent on magnetic field strength, and represents the time taken to lose 63% of the transverse magnetization.[85,86] T2 differences in tissues are emphasized when time between two flip angles is long, a process targeted for developing T2-weighted imaging (T2WI) sequences.[85,86] In inversion recovery sequences, such as fluid-attenuated inversion recovery (FLAIR), a 180-degree preparatory radiofrequency pulse is administered prior to the standard spin echo pulse sequence, causing inversion of the longitudinal magnetization vector.[85] FLAIR is a special type of T2 inversion recovery sequence employed frequently in neuroimaging which uses a prolonged inversion time intended to remove signal originating from the cerebrospinal fluid.[85]

Gradient echo pulse sequences are produced by the administration of multiple acute angle (< 90 degrees) radiofrequency pulses in rapid succession and then reversal of the magnetic field gradient itself to refocus proton spins and generate transverse magnetisation, rather than the 180-degree radiofrequency pulse used in spin echo.[85,86] Similar to spin echo, adjustment of the parameters surrounding administration of the radiofrequency pulses allows production of T1- or T2-weighted images. This technique is more efficient than spin echo and can generally acquire more information in equivalent periods of time.[85] However, gradient echo sequences are more inclined to suffer from magnetic field inhomogeneity and resultant susceptibility artifacts.[85]

Following an initial excitation pulse in gradient echo imaging, an immediate exponential loss of signal amplitude is observed; T2* refers to the decay pattern actually observed by the receiver coil and this is typically of far greater magnitude than standard T2.[85] This difference in magnitude is a function of the inhomogeneity of the magnetic field and may be exploited for imaging purposes. T2* decay underlies all gradient echo sequences, and it allows inherently inhomogeneous tissues – such as the blood seen in cerebral microhemorrhages resulting from the deposition of paramagnetic hemosiderin or deoxyhemoglobin – to be detected more readily.[85] In TBI, such cerebral microhemorrhages have been postulated as being indirect indicators of DAI;[87,88] sequences such as T2*-gradient echo (T2*-GRE) may therefore be hypothesized as more sensitive for the detection of subtle abnormalities representative of DAI than spin echo sequences.[89] Susceptibility weighted imaging (SWI) is another gradient echo sequence which similarly exploits the inhomogeneity of the magnetic field.[90] It indicates, with high sensitivity, the presence of compounds causing local distortions of the field, thus identifying small quantities of hemorrhage or calcium deposition which may be entirely inapparent in other MRI sequences.[91–93]

Application of Magnetic Resonance Imaging Sequences to Neuroanatomy

In assessing neuroanatomy via MRI, standard imaging protocols typically include T1WI, T2WI, FLAIR, and some form of gradient echo imaging, often SWI.[88,94,95] This basic protocol can subsequently be modified based on the specific clinical scenario with the addition of additional sequences or the more detailed modification of imaging parameters.

T1WI provides an excellent overview of the general neuroanatomy, as well as visualization of the soft tissues below the skull base.[88] Fluid, such as cerebrospinal fluid or orbital vitreal fluid, is nulled, appearing dark on this sequence, and the brain's grey matter is darker than the white matter.[94] T2WI allows a more detailed evaluation of the extra-parenchymal areas, including the basal cisterns, the cerebral ventricles, and the subdural spaces and is generally employed to identify pathology.[88] Fluid appears bright on T2WI and the blood flow within vessels may be more readily appreciated. As opposed to T1WI, white matter is darker than grey matter on this sequence.[94] FLAIR is a commonly used sequence in neuroimaging which is similar to T2WI in that grey matter appears brighter than white matter; however, due to the long inversion recovery time used in this sequence, cerebrospinal fluid is nulled, appearing dark, permitting improved visualization of any region where there is parenchyma-cerebrospinal fluid interface which may otherwise suffer distortion on standard spin-echo sequences.[88,94] FLAIR is therefore important for the accurate visualization of the peripheral aspects of the hemispheres and the periventricular edges, in addition to its utility for the assessment of white-matter injury.[88]

While the aforementioned sequences provide a comprehensive appreciation of the brain's overall structure and anatomy, as well as the presence of gross hemorrhage or injury, the further detection of small quantities of blood in the form of microhemorrhages is important for the comprehensive assessment of neurotrauma. The so-called "susceptibility-sensitive" sequences are therefore frequently employed in contemporary protocols for this purpose.[91–93] Such sequences rely on T2*, which is extremely sensitive for detecting local distortions in the magnetic field.[85] T2*GRE and SWI are examples of sequences which exploit this technology, with the latter being the most sensitive for the detection of the products of microhemorrhage such as deoxyhaemoglobin, hemosiderin, and ferritin which are paramagnetic compounds it can potentially differentiate from diamagnetic compounds such as calcium.[88,92,93] Frequently, these minute findings on the susceptibility-sensitive sequences are otherwise inapparent on standard MRI sequences.[96]

Advantages Over Computed Tomography in the Assessment of Neurotrauma

As an imaging tool in neurotrauma, MRI presents several important advantages over CT. These benefits are particularly notable for the evaluation of intracranial lesions, as opposed to extracranial lesions for which CT still remains the dominant imaging tool given its superiority for assessing bone and rapidly identifying fracture in the context of acute trauma.[88,94] More specifically, MRI is superior in many ways, namely to assess

the posterior fossa and the brainstem. However, MRI takes more time to be performed and are not as easily accessible than CT in the acute care setting.

The first commercial MRI systems became available around 1983, with the greater precision of MRI for the evaluation of cerebral lesions in TBI being recognized just a few years thereafter. In as early as 1988, a prospective comparison study[97] between CT and MRI in closed head injury found MRI to be superior to CT in multiple respects, particularly in the detection of non-haemorrhagic parenchymal lesions and brainstem lesions. This study of 40 participants with closed head injury found that early MRI in the acute phase of ICU care was far more sensitive for identifying non-haemorrhagic injury, detecting up to 93.3% of such lesions, whereas early CT identified only 17.7% in the same population.[97] Furthermore, CT was particularly insensitive in the evaluation of brainstem lesions, detecting less than a tenth of such injuries, while MRI was found to identify them at a more than eight-fold higher rate.[97]

Significantly, this substantial difference in accuracy was observed utilizing an early low-field strength 0.5 T MRI machine, employing only the basic T1WI and T2WI sequences.[97] Rapid advances in MRI technology have further widened this gap between the two imaging modalities and more recent studies with contemporary 1.5 T and 3.0 T machines employing more advanced imaging sequences have since confirmed and expanded upon these results. In particular, a recent study[96] employing a standard field-strength 1.5 T machine found that T2WI and FLAIR sequences significantly discriminated between favourable and unfavourable long-term GOS. Unlike CT, T2WI and FLAIR were found to consistently discriminate outcome based on evaluation of lesion volume, volume per lesion and number of lesions. In these same patients, CT's discriminatory ability only reached significance when evaluating volume per lesion.[96] Additionally, high susceptibility sequences, such as T2*-GRE and SWI have also been demonstrated to carry much higher diagnostic yield, often detecting evidence of pathology in patients who otherwise have normal CT scans.[96,98] As these sequences are known to be highly sensitive for the deposition of blood components and thus the detection of microhemorrhage, it has been hypothesized that such findings may represent neuronal shear injury and may therefore correlate with DAI, an important diagnosis with poor prognostic implications.[87,96,99,100]

CT is suboptimal at imaging the posterior fossa due to significant artifacting originating from the osseous structures located in this region.[101] This renders CT images unreliable for diagnosing brainstem lesions, as well as certain posteriorly situated intra-axial lesions. Given the hypothesized importance of brainstem lesions in establishing prognosis following moderate and severe TBI,[102] and the preponderance of such lesions with increasing severity of trauma, it is particularly important to reliably visualize the brainstem with accuracy in neurotrauma patients. Studies on diagnostic accuracy have consistently found that CT imaging detects only a small minority of lesions located in this area.[35,96,103] This is contrary to MRI, on which the brainstem is a site where the presence of lesions has been found to significantly correlate with unfavourable prognosis and is likely

a reflection of increased severity of injury (and possibly related to the mechanism of the impact).[101,103–108] Further underlining the importance of accurate characterization of the location and extent of brainstem lesions, several authors have noted compelling evidence that depth of lesion may have greater prognostic weight than total lesion burden.[101,102,104–107] This is supported by the fact that patients with brainstem lesions generally had poorer outcomes than those with normal brainstems on MRI, regardless of the presence or absence of other more superficially located lesions.[101,104,106,107,109] Such findings imply that accurately characterizing the deepest cerebral lesion present in any given patient is an important factor for the prognostication of TBI via neuroimaging.[101,104–107]

Practical Considerations for Application in Critical Care

As discussed previously, MRI presents several technical advantages over competing neuroimaging methods in regards to image quality, sensitivity and contrast between gray and white matter.[88,94] Notable practical benefits centre on the use of magnetic fields allowing radiation-free image acquisition and the use of gadolinium, rather than iodine, as a contrast agent, which circumvents the possibility of allergic reactions occasionally seen when contrast-enhanced CT is used. Alternatively, there exist several practical pitfalls with the use of MRI which substantially hamper its application in the acute critical care phase of TBI management. The two most significant drawbacks of MRI are the long image acquisition times and the incompatibility of metallic objects within the magnetic fields generated by MRI machines.

In general, cerebral MRI image acquisition is much longer than that of CT scanning. A robust brain MRI examination comprising the full set of sequences for contemporary brain trauma protocols may take upwards of approximately 30 to 45 minutes as opposed to brain CT, which may be completed in the span of just a few minutes.[88] In the acute phase of trauma where patients may be hemodynamically unstable and require advanced monitoring, this length of time has a major impact on the management of TBI patients and may pose an unacceptable risk. The duration of image acquisition is dependent on several factors, but the number of sequences is by far one of the key factors which contributes to increased image acquisition time; acquiring a larger and more diverse range of sequences implies greater length of patient time in the MRI scanner.[88,94] Additionally, given that the majority of TBI patients suffer from elevated intracranial pressure post-trauma, the physical act of leaving such patients supine for the entire duration of image acquisition may be dangerous and potentially aggravate existing lesions.[110] Since radiology facilities are frequently outside of critical care units in most hospitals, transport of a patient with moderate or severe TBI for MRI in the early phase post-trauma implies that patients will need to tolerate a duration of time with reduced medical staff presence and limited monitoring.

Consideration of the constituent sequences in the MRI protocol employed is therefore important for limiting the duration of time required for image acquisition; a balance must be established between the number and type of sequences taken and the duration of scan time which may be tolerated before the risks of the test

outweigh the clinical benefits that an acute phase MRI analysis can offer. Targeted protocols for contemporary 1.5 and 3.0 T machines have now been defined which can acquire a full set of the principle sequences, including a susceptibility-sensitive sequence, in under 20 to 25 minutes.[94] Achieving further decreases in scan time is a topic of active investigation as current targeted protocols remain nevertheless relatively prolonged in the context of critical illness.[111] Ideally, literature in this domain would provide individualized data for each sequence employed and describe the merits of the sequences for outcome prediction based on the types of lesions evaluated in order to more reliably determine which sequences may be omitted from future protocols. Unfortunately, most studies present data that are globally derived from an in-house imaging protocol consisting of an amalgamation of several sequences, which both may vary over time and from centre to centre.[112]

While current image acquisition times remain long, advances in MRI technology are allowing much more efficient imaging protocols and shorter delays in image acquisition.[88,94] Research in moderate and severe TBI specifically is required to identify which MRI sequences are most useful for assessing cerebral trauma within the first few days of injury.[112] Furthermore, studies that validate which sequences best complement one another in an acute phase protocol are required to ensure maximal information with a minimal number of sequences (avoiding repetition).[88,94,112] This refinement of imaging protocols and the feasibility of rapid MRI has already been proven in other forms of neurological disease conceptually similar to TBI. The best example is acute stroke, a neurologic emergency demanding rapid cerebral imaging. Comprehensive MRI stroke protocols taking less than 15 minutes to complete have been described with clinical superiority demonstrated in head-to-head comparisons against CT [113–116]. If a parallel set of sequences could be established for acute moderate and severe TBI, the applicability of MRI in the time directly following hospital admission could potentially rival that of CT.

Beyond the duration of MRI image acquisition, another major barrier to the applicability of MRI for the acute evaluation of neurotrauma is the incompatibility of metallic objects and implants in the magnetic fields of MRI suites.[117–119] As MRI machines generate a magnetic field both within, and in the direct vicinity of the device, gross ferromagnetic objects may become displaced, deformed and possibly airborne. A standard 1.5 T machine generates a magnetic field easily 100 000 times greater than that of the Earth's natural field, within which small magnetic objects may become projectiles drawn towards the machine and larger heavier objects may be shifted or heated.[117–119] This phenomenon poses a danger to both technicians and patients and there have been several cases of death attributed to this phenomenon.[120,121]

Most radiology departments maintain tight safety regulations to ensure that known or potential ferromagnetic objects do not enter within range of MR fields, which also limits the types of medical equipment that can enter the room. This is particularly concerning in the case of TBI patients as such individuals are often under monitoring and ventilator support, with a possible variety of additional support devices, such as intraventricular drains or surgical clips, which are normally compatible with MRI, but also intraparenchymal

devices for ICP monitoring that may not always have industry clearance or regulatory approval for use in MRI. Removal of these and other critical devices for the duration of image acquisition is often either not feasible or potentially not ideal for the management of the patient and can thus delay or outright contraindicate MRI in the very acute phase of care.[110]

The introduction of MRI-safe medical equipment, without ferromagnetic properties, is slowly overcoming this challenge; in particular, the introduction of non-ferromagnetic infusion pumps has allowed more TBI patients to undergo early MRI as they can still receive intravenous fluid support and vasoactive medication to maintain hemodynamic stability during image acquisition.[122]

Current Applications in Patients with Acute Brain Injuries

In neurological emergencies secondary to the occurrence of acute brain injuries such as ischemic stroke, intracranial hemorrhage, or moderate or severe TBI, the use of early neuroimaging in the acute phase is a crucial tool for both establishing the diagnosis and determining the immediate management strategy. While CT has conventionally been employed in this role, the additional (or substitutive) use of early MRI as a highly sensitive imaging modality in the hyperacute (< 6 hours following symptom onset) or acute (first several days after presentation) phase is emerging as a new standard of care in assessing acute brain injuries, in particular stroke.[123] The technical feasibility and safety of employing MRI in the emergency setting of brain injuries has been demonstrated in several studies enrolling patients in the hyperacute phase.[35,113,116,124–127] The use of limited sequences to establish short-duration scan times can be accomplished while maintaining high sensitivity; however, few of these studies have enrolled critically ill patients and their extension to this population still remains largely unknown.

The feasibility of performing MRI in the hyperacute phase for the diagnosis of suspected stroke was best assessed in a large, consecutive, real-world cohort of 356 patients referred for neuroimaging due to suspicion of acute stroke.[125] Following recruitment in the emergency room, these patients underwent both MRI and CT assessment. Comparisons between the two modalities demonstrated the superiority of MRI for the detection of ischemic stroke, with MRI demonstrating the presence of stroke in 46% of patients as opposed to CT, which was diagnostic in solely 10% of cases.[125] Similar superiority of MRI was found when restricting analyses to very early presenters, patients undergoing neuroimaging within three hours of symptom onset, and therefore eligible for thrombolytic therapy. The authors concluded that MRI can feasibly be used as the sole neuroimaging tool in suspected acute stroke,[125] a conclusion supported by other smaller studies which confirm it to be safe as the sole screening method prior to the administration of intravenous thrombolytic therapy.[113,124]

In addition to its application for the accurate early diagnosis of ischemic stroke, the use of brain MRI to assess for the presence of intracranial hemorrhage or hemorrhagic transformation following suspected ischemic

stroke was assessed in the HEME study, a large cohort study over two centres where patients with suspected stroke were recruited to undergo both brain MRI and CT in the hyperacute phase following presentation.[116] This study employed a scan protocol similar to that frequently used in neurotrauma, including T1WI, T2WI, and an obligatory gradient echo sequence, such as T2*-GRE, with a reported total scan duration of only 10 to 15 minutes.[116] Patients were recruited immediately following presentation to the emergency department and all safely underwent MRI. While MRI in the hyperacute phase was found to accurately identify acute hemorrhage in all patients where it was also found on CT, it also identified chronic microbleeds in nearly a quarter of all patients enrolled in the study, all of which were non-apparent on CT and would have been missed if MRI were not performed, leading to the study being stopped early.[116] These findings further build upon prior findings in the German Stroke Competence Network's B5 Hemorrhage Study, where MRI in the hyperacute phase was confirmed to maintain a 100% sensitivity and 100% overall accuracy for the identification of hemorrhage as compared with CT in the hyperacute phase, further suggesting this modality could supplant the need for CT altogether in acute stroke.[128]

Translation of these findings from the acute stroke or intracranial hemorrhage population to patients with acute moderate or severe TBI is challenging, as the latter group of patients are typically critically ill and may be frequently unstable at the time of presentation. Initial neuroimaging in this population focuses on the determination of the presence or absence of neurosurgical indications (such as the management of fractures or need for evacuation of gross hematomas), and thus CT imaging is the most widespread modality employed in the first 24 hours following TBI.[98,129–131] In line with this, the Brain Trauma Foundation guidelines for the management of acute TBI base recommendations for surgical intervention on CT findings alone.[48] While no studies have examined the use of MRI in the hyperacute setting post-TBI (or as the initial neuroimaging modality), several studies have examined the feasibility and yield of undertaking early MRI within the first few days following trauma.[35,36,127] All of these studies feasibly and safely managed to undertake MRI within 24 to 72 hours following TBI; patients were described as sedated and heavily monitored throughout the course of MRI acquisition, and no adverse events related to the imaging procedure were reported in any of the studies. All studies reported findings on early MRI which correlated with long-term (>6 months) mortality and neurological outcome. Specifically, brainstem lesions consistent with shear injury identified on MRI as early as 24 hours after moderate or severe TBI were independently predictive of long-term outcome,[35] raising the possibility that acquiring such detailed prognostic information early in the clinical course may help guide acute management and level-of-intervention decision-making on the part of clinicians and substitute decision makers.

Potential Applications in Patients with Traumatic Brain Injury

There is considerable practice variation in MRI timing and image protocols employed following TBI coupled with frequent uncertainty regarding the prognostic implications of many lesion patterns encountered.

The current clinical practice guidelines and recommendations for the use of neuroimaging in TBI were updated most recently in 2015,[130] prior to the conduct of our systematic review, and provide a class I recommendation for the use of CT as the first line imaging modality in the acute phase of moderate or severe TBI. Recommendations on the use of early MRI are vague; MRI is deemed indicated in the event where the CT findings are normal or out of proportion to, a clinically persistent, unexplained, neurological findings (class I recommendation).[130] The use of MRI with high susceptibility sequences, such as T2*-GRE and SWI, is given a class IIa recommendation in the early phase of moderate or severe TBI, with acknowledgement of its high sensitivity for establishing the diagnosis of shear injury consistent with DAI, but also a note of the lack of conclusive published data examining the relationship such findings with long-term clinical outcome and the need for further research.[130]

An improved understanding of the role of early MRI in the prognostic assessment of moderate and severe TBI is therefore required in order to both establish its appropriate application in this context and comprehend the predictive value of the lesion patterns identified. Addressing such uncertainties in the current clinical practice guidelines is thus a principle objective of this thesis and the research question we address in our study. While MRI data was not studied in the original IMPACT database,[65] a large volume of research has been published on its use for prognosticating moderate and severe TBI, encompassing variable scan times post-TBI and diverse imaging protocols, some with emphasis on the use of susceptibility sensitive sequences for the detection of lesions considered beyond the scope of CT imaging.[35,96]

Given the expected large breadth of studies on this subject and the need to comprehensively assess all published MRI lesion patterns with potential prognostic value, the use of systematic review methodology is crucial for the identification of all studies potentially relevant to this research question and thus avoid an unbiased assessment of evidence.[132] Undertaking subsequent quantitative synthesis via meta-analysis will permit the simultaneous maximization of statistical power, aiding in the determination of prognostic associations between MRI and clinical outcome, and the identification of areas of conflicting evidence or heterogeneity requiring future study.[132] In conducting this systematic review and meta-analysis, the objectives of this thesis are to comprehensively summarize all existing evidence, assess the methodological quality of studies underlying the data, and guide the conduct of future high-quality studies in areas where inadequate data exists.

Prognostic Systematic Review Methods

Introduction

Traditional systematic reviews of interventions with pairwise meta-analysis typically aim to synthesize all existing data (usually randomized) for a single treatment, compared to a control or placebo, for a pre-defined outcome.[132] Extending these original methods to other primary epidemiological study designs is an ongoing

priority of the Cochrane Collaboration, which oversees, centralizes, and guides the process of expanding systematic review methodology.[133] Whilst the design of the primary studies assessed and synthesized in non-conventional systematic reviews may differ based on the original research question, the basic methodologic framework remains largely unchanged. As with systematic reviews of interventions, the major steps in undertaking a prognostic systematic review include: identifying the research question, designing and conducting a systematic literature search, abstracting and organizing the relevant data, undertaking quantitative synthesis (if applicable), appraising risk of bias, and grading of the quality of evidence and strength of conclusions.[134] However, the tools used for each step of this process and their application to the primary literature require their adaptation to the methodology of prognosis research in order to optimize their applicability and validity in this field.

Primary prognosis research has the fundamental aim to provide data on the clinical course, natural history, or long-term outcomes of populations with specific diseases or conditions.[135] Furthermore, data from prognostic studies can be employed to predict the likelihood of a particular outcome in specific individuals via the derivation and validation of statistical models.[135,136] As individual prognosis studies often present diverging or inconsistent findings, increasing numbers of systematic reviews attempting to synthesize their findings and assess their methodological quality are being published, often with suboptimal methodology or reporting.[137] To address this growing need for uniform methodology, and as an adjunct to conventional systematic review and meta-analytic methods, the Cochrane Collaboration's Prognostic Methods Group was established in 2006 as a new methodological working group.[138] It aims to both construct standards for improving the validity and precision of prognostic systematic reviews, as well as improve the reporting of the published primary prognosis literature.[136,139]

Within prognosis research, the Prognosis Research Strategy (PROGRESS) group defines three principle study designs which comprise the bulk of prognosis research.[140] These comprise: studies investigating the outcomes of health-related conditions in a set population over time ("fundamental prognostic research"), the derivation and validation of statistical models which predict the risk of a future outcome in an individual ("prognostic model research"), and the investigation of specific factors associated with prognosis ("prognostic factor research").[140–142] The methods for searching, quantitatively pooling, and judging risk of bias are distinct between prognostic factor and prediction model studies.[136,143–145] Notably, prognostic factor studies relate each individual prognosticator with outcome, typically employing a measure of association, while validation studies of prediction models present overall model performance statistics (such as discrimination or calibration).[134] As this thesis focuses specifically on the determination of which brain MRI findings may be individual prognostic factors related to mortality and neurological outcome in patients with moderate or severe TBI, the discussion of clinical

prediction model studies is beyond its scope and the subsequent sections on prognostic systematic review and meta-analysis methods will focus specifically on the search and synthesis of prognostic factor studies.

Prognostic Systematic Review Search Methods

In contrast to systematic reviews of interventions, undertaking a prognostic factor systematic review and meta-analysis implies the identification of observational cohort studies, the methodological design typically employed to study prognosis in defined populations over time.[140,141] Major health research databases such as MEDLINE and EMBASE generally have robust indexation for randomized studies of interventions, in turn lending to the more straightforward and simple design of high accuracy validated search filters for primary studies of randomized trials.[146–149] In contrast, observational cohort studies (and by extension studies of prognosis) have less detailed or easily navigable indexation, in part due to the variability of their study designs and the only recent development of consensus definitions to standardize their methodology and reporting.

To address this gap in methodology for systematic reviews of prognostic studies and to address the large volume of citations returned by text terms search alone, the Hedge's Project undertaken at McMaster University's Health Research and Information Unity has developed search filters specific to prognostic factor studies validated against a gold standard of hand searching and human review.[150] High sensitivity search strategies specific to prognostic studies therefore exist for searching within MEDLINE[151,152] and EMBASE,[152,153] albeit with far lower rates of precision than their counterparts designed for studies of therapy,[146] therefore leading to higher volume overall of retrieved citations for title and abstract review. While similar formally validated filters for other major health research databases, such as BIOSIS, do not yet exist, our team's in-house combination and conversion of indexing terms found in the MEDLINE and EMBASE search filters permitted the design of a novel filter specific to BIOSIS to serve as an adjunct to the two main prognostic search filters.

Prognostic Meta-Analysis and Evidence Synthesis

Statistical methods for the pooling of aggregate data in univariable prognostic factor meta-analysis are similar to those employed for traditional pairwise meta-analysis of randomized studies of intervention. This requires the reviewers to extract, from each study, either dichotomous data on outcomes for each group with or without the prognostic factor (e.g. the number of participants who did or did not die among those with or without a specified lesion pattern on MRI, such as in the study conducted in the purvey of this thesis) or an estimate of the relationship between the prognostic factor and the defined outcome measure (e.g. the risk ratio for all-cause mortality in patients with TBI) with this estimate's standard error (e.g. the standard error of the log risk ratio, or a method for calculating this such as the confidence intervals of the measure of association).[132] Weighted data synthesis can then be undertaken using either the inverse variance or Mantel-Haenszel methods to generate pooled risk ratios with confidence intervals. Given that prognostic research is conducted in observational cohorts

that may vary significantly based on the population they were sampled from, the assumptions required for fixed-effects analysis models generally do not hold and random-effects models should be employed exclusively.[154]

Beyond quantitative data analysis, evidence synthesis in meta-analysis also implies the critical appraisal of the underlying studies contributing to the pooled results. The Cochrane Collaboration suggests that the methodological quality of each primary study included in a systematic review and contributing data to the pooled results requires formal assessment for potential sources of bias, typically undertaken with a risk of bias tool.[155] Subsequently, an overall judgement on the level of confidence in the quality of the evidence leading to the scientific conclusions drawn from each meta-analysis should be performed, usually via the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is now considered a standard in determining strength of recommendations.[132,156–159] In both these processes, the underlying methodology was initially designed for studies of intervention, typically assuming the targets of appraisal would be randomized trials of therapy; in prognostic factor systematic review, specific methodological adaptions must therefore be employed, adjusting judgments of bias or confidence to standards specific to this field and study type.

Published initially in 2006[160] and updated in 2013,[161] the Quality in Prognostic Studies (QUIPS) tool has been developed and specifically validated for application to prognostic factor studies and is the most robust tool for assessing the risk of bias of included studies in systematic reviews and meta-analyses. In studies of prognostic factors, QUIPS critically appraises validity across six domains which may introduce bias: participation, attrition, prognostic factor measurement, confounding, outcome measurement, and analysis and reporting.[161] Reviewers acting as assessors make a judgement of low, moderate, or high risk of bias for each domain and at least two assessors are suggested to examine each study to form a consensus for each domain. Although not explicitly advocated by the tool's developers, an overall judgment on a study's risk of bias may be made by the two assessors, in weighing the final ratings of each of the domains.

Prior to the availability of QUIPS, no validated tool existed for assessing risk of bias in prognostic factor studies. Adaptation of tools and checklists created to assess other forms of observational study designs were therefore alternative options for this task; the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)[162,163] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[164,165] represented two such references previously used to create a standardized tool for prognostic systematic reviews in our institution prior to the availability of a final QUIPS tool.[166] Despite the availability of QUIPS, the final risk of bias assessment strategy employed for this thesis also included the integration of selected searching questions from the QUADAS-2 and STROBE tools to both improve the robustness of risk of bias evaluation for each individual domain, but to also increase the emphasis on reporting quality, an area which in QUIPS is only

represented in a single domain.[161] A final version of the adapted risk of bias tool used in this systematic review and meta-analysis is provided (sections *1.9 Appendix 2* and *2.13 Appendix 2*).

Assessing the level of confidence in effect estimates derived from analyses in prognostic factor systematic reviews is fundamentally different from studies of intervention where randomized, controlled trials are considered the benchmark for high-quality evidence and reports of observational studies are downgraded.[167] In the adaptation of GRADE methodology for prognostic factor systematic reviews,[168,169] observational evidence is recognized as beginning as high quality in the field of prognosis. Once this "phase of investigation" is determined, confidence can be subsequently rated down when evaluating the five GRADE domains of risk of bias, imprecision, inconsistency, indirectness, and publication bias, any one of which representing situations where quality of evidence may be compromised.[168,169] Although routinely employed when assessing evidence in studies of intervention, the domains for rating up confidence (such as large effect size or exposure-response gradient) are less frequently applied to rating prognostic effect estimates as the definitions of when these become significant enough to be considered applicable is less well-defined in the prognostic literature.[168]

Chapter 1: The Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis Protocol

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1.1 Résumé

Introduction : Le traumatisme craniocérébral (TCC) est une condition aux conséquences dévastatrices avec un taux de mortalité et de morbidité élevés à long terme. Malgré le besoin d'indicateurs pronostiques objectifs permettant de guider la prise en charge clinique initiale, il existe peu des facteurs pronostiques utiles dans la phase aiguë. L'imagerie par résonance magnétique effectuée tôt durant la prise en charge a été étudiée comme outil pronostique, mais des doutes demeurent quant à sa valeur prédictive et sa capacité à distinguer quels types de lésions détectées en phase aiguë sont corrélés avec des issues cliniques à long terme.

Méthodes : Nous entreprendrons une revue systématique d'études observationnelles de cohorte et d'essais cliniques randomisés chez les patients adultes ayant subi un TCC modéré ou grave chez lesquels une IRM cérébrale a été effectuée au cours de la phase aiguë de soins. Une stratégie de recherche ayant une sensibilité élevée sera employée dans les bases de données MEDLINE, EMBASE, BIOSIS, et Cochrane CENTRAL pour identifier les études. Deux réviseurs procéderont indépendamment à une sélection des références identifiées pour en déterminer l'éligibilité et extraire les données à l'aide d'un formulaire standardisé. Si la méta-analyse est possible, les données quantitatives pour chaque issue clinique seront analysées pour chaque type de lésion par des modèles à effets aléatoires exprimées en risque relatif par la méthode Mantel-Haenszel. L'hétérogénéité sera évaluée par la valeur statistique I^2 et le risque de biais sera évalué avec des échelles standardisées. Des analyses de sous-groupes sont planifiées en fonction de la gravité du TCC, le délai de l'IRM post-TCC, l'amplitude du champ magnétique, les séquences IRM, le délai de l'évaluation de l'issue clinique, et du risque de biais des études.

Discussion : Nous nous attendons à une hétérogénéité clinique importante étant donné que les études éligibles couvriront des périodes différentes de l'évolution de la technologie en IRM, et incluront probablement une variabilité importante des protocoles de séquences d'images et des délais d'acquisition post-traumatisme. Sur la base des études existantes, nous prévoyons que les lésions détectées dans le tronc cérébral auront une valeur prédictive importante. Notre revue systématique permettra aux cliniciens d'interpréter avec une meilleure précision l'IRM dans le contexte pronostique des patients atteints de TCC modéré ou grave et d'informer les chercheurs dans ce domaine afin d'améliorer la méthodologie des études futures.

Enregistrement de la revue systématique : Prospero CRD42015017074

1.2 Abstract

Background: Traumatic brain injury (TBI) is a devastating condition with significant long-term mortality and morbidity. Despite current need for objective indicators to guide initial decision-making, few reliable acute phase prognostic factors have been identified. Early magnetic resonance imaging (MRI) has been investigated as a prognostic tool, but uncertainty remains in both its discriminative predictive value and which acute phase lesion patterns correlate with long-term outcome.

Methods: We will conduct a systematic review of observational cohort studies and randomized controlled trials of adult moderate or severe TBI patients who underwent MRI in the acute phase after trauma. A high sensitivity search strategy will be employed in MEDLINE, EMBASE, BIOSIS, and Cochrane CENTRAL to identify citations. Two reviewers will independently screen all identified references for eligibility and extract data into a standardized form. Data will be collected on study design, baseline demographics, trauma characteristics, magnetic resonance (MR) technical specifications, lesion patterns, and outcomes as related to acute MRI imaging. If meta-analysis is possible, quantitative data for each outcome will be pooled per type of lesion pattern using random effects models and expressed as Mantel-Haenszel relative risks in order to determine the prognostic value of lesions detected on acute MRI and their strength as discriminatory predictors of long-term outcome. Statistical heterogeneity will be evaluated with the I_2 statistic, and risk of bias and reporting quality will be assessed with standardized scales. Subgroup analyses are planned as a function of TBI severity, MRI-timing post-TBI, MRI field strength, MRI sequence, timing of outcome assessment, and risk of bias.

Discussion: We expect significant clinical heterogeneity, as eligible studies will likely encompass different periods in evolving MRI technology in addition to significant variability of image sequence protocols and timing of acquisition between centers. Based on existing studies in TBI, we expect lesions detected in the brainstem to be of significant predictive value. Our systematic review will allow clinicians to more accurately interpret MRI in the context of determining prognosis for moderate and severe TBI patients and inform researchers in this domain to improve the methodology of future studies.

Systematic review registration: Prospero CRD42015017074

1.3 Background

Traumatic brain injury (TBI) is a significant global health problem, with the 1.7 million cases occurring annually representing upwards of $60 billion of direct and indirect health care costs in the USA alone [1, 2]. Moderate and severe TBI are most often life-threatening conditions requiring immediate intensive care. The determination of long-term neurological prognosis is thus of importance as it may inform patients or their representatives and better guide critical level of intervention decision-making [3]. Few reliable prognostic factors currently exist in this domain, with the large-scale IMPACT study identifying only age, pupillary reactivity, and the motor subscale of the Glasgow Coma Scale (GCS) as independent predictors of outcome [4, 5]. Recently, certain biomarkers [6] have also shown promise as outcome indicators; however, none of these factors are presently appropriate for clinical use.

Computed tomography (CT) currently plays a pivotal role in the immediate post-injury work-up where gross lesion characterization and indications for urgent surgical intervention must be rapidly established [7]. In the last four decades, magnetic resonance imaging (MRI) has emerged as a highly sensitive imaging tool in TBI. Its superiority compared to CT in detecting cerebral lesions in TBI, particularly non-hemorrhagic lesions and lesions localized to the posterior fossa, became evident just a few years following its clinical availability [8]. Visualization of the brainstem is especially crucial as a large volume of evidence from animal [9] and histological [10] studies have demonstrated that deeper, more caudally located lesions are correlated with greater severity of trauma. In continuity with this centripetal model [9] of brain injury, it has been proposed that such deeper lesions also have a greater significance on long-term outcome and may serve as prognostic indicators [11, 12]. Though several setbacks such as long imaging times and incompatibility of metallic objects have limited its use, advances in magnetic resonance technology are rapidly overcoming these obstacles giving MRI a growing role in the acute phase evaluation of TBI.

Over the last several decades, numerous studies have investigated the predictive value of MRI lesions. Owing at least in part to the diversity of approaches possible in interpreting cerebral lesions induced by TBI and correlating them to unfavorable long-term outcome, the results of such studies have been variable to date and at times contradictory. We seek to systematically identify all studies in this domain and to methodically synthesize their data studying MRI as a prognosticator in moderate and severe TBI. Our primary objective is to determine the prognostic value of MRI in TBI by identifying the lesion patterns that significantly correlate with mortality and neurological outcome. We also seek to investigate sources of possible heterogeneity and evaluate the methodological quality of the included studies.

1.4 Methods

1.4.1 Design

A team of experts including intensivists, internists, epidemiologists, and a biostatistician collaborated to develop the research question and study design of this systematic review, in accordance with the methodological guidelines delineated in the Cochrane Handbook for Systematic Reviews and Meta-Analyses [13]. This protocol was registered in PROSPERO (CRD42015017074). The final manuscript will be written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [14].

1.4.2 Information Sources and Search Strategy

MEDLINE, EMBASE, BIOSIS, and the Cochrane Central Register of Controlled Trials (CENTRAL) will be systematically searched from their inception, with an update planned before submission for publication. A three-pronged search strategy maximizing sensitivity has been developed to identify studies investigating MRI as a prognostic tool in TBI. Free text keywords, as well as Medical Subject Heading (MeSH) and Emtree terms, linked with the Boolean operator "OR" were used to design each prong of the search strategy, with the three prongs linked with the operator "AND." All strategies will be reviewed by an information specialist (health care librarian) for robustness. After selection is complete, the reference lists of included studies will be reviewed to identify any additional eligible studies. An example of our search strategy is provided (Appendix 1).

1.4.3 Eligibility Criteria and Study Selection

The following inclusion criteria will be utilized to determine study eligibility: (1) cohort studies and randomized controlled trials (2) investigating the prognostic value of standard structural MRI (3) performed in the acute phase (≤28 days post-trauma) (4) of moderate or severe TBI (≥50 % with GCS ≤12) (5) in an adult population (≥80 % of patients aged ≥18 years old) (6) reporting at least one of our outcome measures of interest (mortality, Glasgow Outcome Scale (GOS), or extended Glasgow Outcome Scale (GOSe) as defined below). Studies with a significant population (>10 %) of penetrating TBI will be excluded. There will be no restriction based on publication date or language; translators will be consulted for articles published in languages other than English or French.

Two blinded reviewers will perform screening for study eligibility independently in a two-step process. Retrieved citations will initially be screened by title and abstract review for potential eligibility; retained studies will then be assessed by full-text analysis to confirm inclusion in the systematic review. A third reviewer will be consulted for arbitration in case of discordance. Reasons for exclusion at the full-text stage will be recorded and presented for transparency.

1.4.4 Data Collection

Two reviewers will independently extract data into a standardized data abstraction form, with a third to be consulted in cases of discordance. The following set of data will be extracted from each study: (1) study design, such as year, setting, study type, sample size, duration of follow-up, inclusion and exclusion criteria, sources of funding, and conflicts of interest; (2) patient characteristics, such as age, sex, comorbidities, and mechanism of injury; (3) therapeutic and supportive measures, such as use of mechanical ventilation, intracranial drains, and surgical intervention; (4) characteristics of the magnetic resonance imaging modality, such as time to scan, field strength, brand, sequences taken, and image plane; and (5) measures of outcome presented in relation to MRI image characteristics, such as lesion localization, lesion type, lesion size, and radiological scores, stratified by image sequence when possible. The initial data abstraction form will be piloted on five studies to ensure robustness, with subsequent modifications for thoroughness if necessary.

To avoid duplication, if the same study is published more than once, either the most complete article will be retained or all articles will be extracted and presented as a single study in analyses.

1.4.5 Assessment of Methodological Quality

The methodological quality of any randomized controlled trials (RCTs) included in this systematic review will be evaluated with the Cochrane Collaboration's risk of bias tool [13]. However, given that this is a prognostic systematic review and that we predict that the majority of the studies eligible for this review will have observational cohort designs, we modified the Quality in Prognostic Studies (QUIPS) tool [15] to develop a 26-item checklist appropriate for the evaluation of the risk of bias of such studies (see Additional file 2 for the complete tool). The QUIPS tool is a validated method for assessing the risk of bias in prognostic factor studies; we supplemented its list of searching questions with excerpts from the QUADAS-2 tool [16, 17] for additional rigor as we felt that neither framework alone encompassed all relevant questions regarding risk of bias. The STROBE statement's [18] 22-item checklist will be used to evaluate the reporting quality of the included studies. By performing these assessments independently and in parallel, we seek to differentiate between methodological bias and omissions in reporting in the primary studies. Summaries of these evaluations will be presented in a graphical format to offer precise recommendations for future studies in this domain and, in the case of the risk of bias assessment, to also guide subgroup analysis. Both risk of bias and reporting quality evaluations will be performed independently by two reviewers.

1.4.6 Quality of Evidence

An adaptation of the GRADE framework for prognostic studies [19] will be employed to judge the quality of evidence for each outcome reported in this systematic review.

1.4.7 Outcomes

Our primary outcomes will be mortality and unfavorable long-term Glasgow Outcome Scale (GOS or GOSe), defined as either a GOS of 1–3 or a GOSe of 1–4. Our secondary outcomes include duration of hospital stay, duration of ICU stay, any reported scales employed by the included studies to determine patient function (such as the Disability Rating Scale (DRS), the Craig Handicap Assessment and Rating Technique (CHART), and mini-mental state examination (MMSE)), and all other possible clinical end-point measures (such as coma duration, probability of readmission, and duration of rehabilitation).

1.4.8 Statistical Analysis and Data Synthesis

Data will be presented in a descriptive manner. Nominal variables and count data will be reported using proportions while continuous variables will be presented as either means with standard deviations or medians with ranges, depending on what is reported in the primary studies. If reported, effect measures will be presented in both their adjusted forms and unadjusted forms where possible. The number of studies reporting each type of lesion pattern in relation to outcome will be reported.

If meta-analysis is possible, random effects models will be employed. Dichotomous outcomes will be presented as risk ratios (RR) with accompanying 95 % confidence intervals (CIs) and forest plots, as generated with the Mantel-Haenszel method using Cochrane Review Manager version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark, 2012). Data from the mortality and GOS will be presented at hospital discharge, 3, 6, and 12 months or beyond, according to the availability of the data.

Ordinal data will be presented in tabular format, with risks and relative risks for each study accompanied by 95 % CIs calculated using exact formulas. P values for global and trend tests will be computed for each study using SAS 9.3 (SAS Institute Inc., Cary, NC, USA, 2011). Ordinal data from radiological scores will also be dichotomized, when possible, according to the presence or absence of brainstem lesions and pooled using the same meta-analytical methods for dichotomic data as described above.

Heterogeneity will be evaluated by the I_2 statistic and interpreted via the recommended standard categorization of negligible (<40 %), moderate (30–60 %), substantial (50–90 %), or considerable (75–100 %) [13]. Where permitted by the data available, sensitivity and subgroup analyses will be undertaken to explore sources of heterogeneity and test the robustness of the results. Such analyses will be performed in regard to minimal age of inclusion, severity of TBI, timing of MRI post-TBI, MRI field strength, MRI sequence, timing of outcome assessment, inter-rater reproducibility of image analysis, timing of outcome assessment, rehabilitation strategies, and study risk of bias. Visual analysis of funnel plots will be used to evaluate the presence and degree of publication bias.

1.5 Discussion

Determination of long-term prognosis is an important step in the acute evaluation of moderate and severe TBI patients, particularly since a large proportion of such patients are young [1] with few or no comorbid conditions. Although a significant body of evidence has shown that MRI is superior to CT in detecting most types of traumatic parenchymal lesions [8, 20], only the latter is currently routine whereas use of the former remains sporadic in the acute phase. While the presence of several different lesion types, particularly those attaining the brainstem, has been correlated with severity of trauma [9, 10], the role of employing sensitive imagery such as MRI as an early prognosticator is not yet clear. In TBI patients, doubt remains concerning both the discriminatory ability of early MRI as well as which specific lesion patterns yield the highest prognostic information.

This project seeks to identify, class, and synthesize all existing original research with data relating lesions identified on acute MRI to clinical outcome in moderate and severe TBI patients. Our proposed systematic review of prognostic studies is based on well-recognized methodological [13, 16] and reporting [14] recommendations. It will determine the lesion patterns and radiological characteristics identifiable on acute MRI that correlate with the long-term outcome of patients having suffered moderate or severe TBI. By summating all existing evidence in the domain, the results of this systematic review will thus seek to conclusively inform clinicians and decision-makers on the significance, if any, of information provided by acute MRI in TBI and to explicitly establish its pertinence in the early management of moderate and severe TBI. Furthermore, by methodically classifying existing evidence and evaluating its risk of bias, our review seeks to also inform investigators of future studies in order to improve consistency in the approach to image interpretation and establish areas where further research is required.

Despite our intention to use a rigorous methodology and to employ a widely accepted statistical model for data analysis, we expect to likely encounter elevated clinical and statistical heterogeneity in the majority of our primary analyses. We anticipate this variability due to several factors, the most notable being that we expect that the majority of included studies will be of an observational cohort design. The pool of eligible studies will likely also encompass a significant variability in technical characteristics, due to both the evolution of MRI technology since its clinical introduction, as well as differences in sequence protocols and timing of imaging between study centers. Moreover, the method of image interpretation and lesion characterization is often variable, making it difficult to compare results across studies. To address such concerns regarding methodology, this systematic review will provide a global analysis of the quality of the evidence through the evaluation of both the risk of bias and the reporting quality of all the included studies via standardized assessment tools. The final resultant of this review will thus be both a systematic aggregate of the evidence that exists on the subject of prognostication in TBI via MRI as well as a critical appraisal of the methodology employed in this domain to

ultimately also improve the quality of future studies. Our team plans to disseminate the results of the systematic review via presentation at research conferences and by publishing the results in a peer-reviewed journal.

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1.8 Appendix 1: Example of MEDLINE Search Strategy

1. ((brain[TIAB] OR brains[TIAB] OR brainstem*[TIAB] OR head[TIAB] OR heads[TIAB] OR craniocerebral*[TIAB] OR intracrani*[TIAB] OR intra-crani*[TIAB] OR intercrani*[TIAB] OR inter-crani*[TIAB] OR cerebr*[TIAB] OR cerebel*[TIAB] OR forebrain*[TIAB]) AND (injury*[TIAB] OR injuries[TIAB] OR injured[TIAB] OR trauma[TIAB] OR traumas[TIAB] OR traumatic*[TIAB] OR traumato*[TIAB] OR damag*[TIAB])) OR TBI[TIAB] OR Craniocerebral Trauma[MeSH:NoExp] OR

Brain Injuries[Mesh:NoExp] OR Brain Hemorrhage, Traumatic[Mesh] OR Diffuse Axonal Injury[Mesh:NoExp] OR Coma, Post-Head Injury[Mesh:NoExp] OR Head Injuries, Closed[Mesh:NoExp] OR Intracranial Hemorrhage, Traumatic[Mesh]

2. magnetic resonanc*[TIAB] OR “diffusion weighted”[TIAB] OR “diffusion tensor”[TIAB] OR MRI[TIAB] OR MR[TIAB] OR fMRI [TIAB] OR dMRI[TIAB] OR MRS[TIAB] OR MRA[TIAB] OR DTI[TIAB] OR DWI[TIAB] OR “T1- weighted”[TIAB] OR “T1 weighted”[TIAB] OR T1WI[TIAB] OR T1[TIAB] OR T1rho[TIAB] OR “T2-weighted”[TIAB] OR “T2 weighted”[TIAB] OR T2WI[TIAB] OR T2[TIAB] OR “T2*-weighted”[TIAB] OR “T2*WI”[TIAB] OR “T2*”[TIAB] OR “T2*-Gradient Echo”[TIAB] OR “T2*-GRE”[TIAB] OR “Fluid attenuated inversion recovery”[TIAB] OR FLAIR[TIAB] OR “Susceptibility weighted”[TIAB] OR SWI[TIAB] OR

“Magnetic Resonance Imaging”[MeSH:NoExp] OR “Diffusion Magnetic Resonance Imaging”[MeSH:Exp] OR “Echo-Planar Imaging”[MeSH:NoExp] OR “Magnetic Resonance Angiography”[MeSH:NoExp] OR “Magnetic Resonance Imaging, Interventional”[MeSH]

3. Incidence[MeSH:NoExp] OR Mortality[MeSH Terms] OR Follow Up Studies[MeSH:NoExp] OR pognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]

4. #1 AND #2 AND #3

5. animals[MeSH] NOT humans[MeSH]

6. #4 not #5

1.9 Appendix 2: Evaluation of Risk of Bias

Domain	Description	Judgment	Risk of bias	Applicability concerns
01. Study Participation				
Was consecutive or appropriate random sampling used to enroll patients? (As opposed to voluntary sampling)	*Describe methods of patient selection* *Describe included patients (previous testing, presentation, intended use of index test, and setting)*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was there adequate participation in the study by eligible individuals?	Low risk if: - Majority (≥85%) of individuals meeting eligibility criteria participated in study	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was a case-control design avoided?	Low risk if: - Consecutive or random selection *Careful in distinguishing bias vs. applicability concerns: judgement call	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Did the study avoid inappropriate exclusions?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the included patients do not match the review question?	- All adult (no paediatric) population - Moderate or severe - All pathologies are TBI - Blunt head injury (no penetrative)	□ Adults □ Moderate or severe □ Blunt TBI		
Overall	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between the prognostic factor and outcome	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
02. Prognostic Factor Measurement				
Blinding Were the prognostic marker results interpreted without knowledge of clinical data?	*Describe the prognostic marker and how it was conducted and interpreted*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was the method of prognostic factor measurement adequately valid to and reliable to limit misclassification bias?	Low risk if: - Method of measurement recognized as valid or standard of practice in the domain - Information on reliability/validity of method of measurement presented (ex. Cohen's kappa, etc.) - Diagnostic criteria presented	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Inter-rater agreement Was inter-rater agreement evaluated via a statistical measure (ex. Cohen's kappa)?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	

If a threshold was used, was it specified *a priori*? [□ Not applicable]		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were diagnostic criteria for prognostic factors well-defined?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the prognostic marker, its conduct, or its interpretation differ from the review question? (including timing of assessment)	Low risk if: - The method and setting of measurement of the prognostic factor is the same for all participants Applicability concern if: - Prognostic marker not associated to specific sequence (applicability issue; bias unlikely to be affected) - Prognostic marker (MRI) measured over very long period	□ Specific sequence □ Measured at specific time or over a short time window	□ High □ Low □ Unclear	
Overall	The prognostic factor is adequately measured in study participants to sufficiently limit potential bias.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
03. Outcome Measurement				
Was the outcome measurement adequate (evaluated reliably and validly)?	*Describe the outcome measurement and how it was conducted and interpreted*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all patient outcomes evaluated identically? (method/setting standardized)	Low risk if: - Data on reliability/validity - Similar method of evaluation for all subjects - Outcome evaluator blinded to patient history	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Blinding Were the outcome results interpreted without knowledge of the results of the prognostic markers?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the prognostic marker, its conduct, or its interpretation differ from the review question? (including timing of assessment)	Applicability concern if: - Outcome measure reported as a binomial variable with a cut-off different from our review - Outcome is measured or timing reported over very long intervals - Minimum 1 measure of outcome at ≥6 months post-TBI	□ Same cut-off □ Specific timing of assessment or short time window □ Minimum of 1 measure at ≥6 months post-TBI		
Overall	The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear

04. Study Attrition				
Was the response rate (proportion of baseline sample completing the study and providing outcome data) adequate? Are there subjects not included in the analysis?	Low risk if: - < 15% lost to follow-up - Loss to follow-up but with multiple imputation method - Intent-to-treat analysis	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all subjects included in the analysis? (Loss to follow-up? Withdrawal? Subjects not tested? Missing data? Etc.)		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were attempts made to collect information on participants who dropped out or were lost to follow-up?	Reasonable attempts were made by investigators to acquire information on participants who did not complete the study and characterize them	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are baseline characteristics and outcomes similar in patients who completed the study compared to those who did not?	Low risk if: No important differences between participants having completed the study and those who did not	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The loss to follow-up or missing data affects a small proportion of the study participants and is not associated with key characteristics sufficient to limit potential bias to the observed relationship between the prognostic factor and outcome	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
05. Timing				
Was there an appropriate interval between the prognostic marker and the outcome measurement? (Biologically plausible, sufficient duration for outcome to occur)	*Describe the interval between prognostic markers and the outcome measurement* Low risk if: - Mortality or GOS measured at hospital discharge or later	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The interval of time between measurements of the prognostic factor and outcome is adequate to respond to the study hypothesis	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
06. Study Confounding				
Did the study adequately control for potential confounders?	*Describe any method used to control for potential confounding*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	

Are important potential confounders accounted for in the analysis?	Low if: - Adjustment for: age, motor subscale of the GCS, and pupillary reactivity High if: - No adjusted measure reported - Inadequate adjustment (important variables not taken into account, improper statistical method used (ex. forward model))			
Are the measurements of all important confounders adequately valid and reliable?	Method of measurement recognized as valid or standard of practice in the domain The method and setting of confounding measurement are the same for all study participants	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between the prognostic factor and outcome.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
07. Statistical Analysis				
Are the statistical methods employed in the study adequate?	The statistical tests/methods are appropriate for the type of data analyzed and are adequate for testing the study hypothesis	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Is the model development strategy adequate (if applicable)?	The strategy for model building is appropriate and is based on a conceptual framework or model The selected statistical model is adequate for the design of the study.	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all statistical analyses pre-specified?	Low if: - No post-hoc data analysis Reviewer's judgement if: - Post-hoc analysis clearly identified as such and adequately justified in discussion	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The statistical analysis is appropriate for the design and hypothesis of the study, limiting potential for invalid or spurious results.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear

Modified from:

- Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine*. 2013;158(4):280-6.
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Chapter 2: The Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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2.1 Résumé

Objectifs : Le traumatisme craniocérébral (TCC) constitue une cause majeure de mortalité et d'incapacités. Cependant, la plupart des indicateurs pronostiques ne sont pas suffisamment précis pour guider la prise en charge initiale. Bien que l'imagerie par résonance magnétique (IRM) soit de plus en plus utilisée dans la phase aiguë du TCC, sa valeur pronostique reste incertaine. Nous avons donc entrepris une revue systématique et méta-analyse des études évaluant la valeur prédictive des lésions identifiées sur l'IRM aiguë pour la prédiction d'issue clinique des patients ayant subi un TCC modéré ou grave.

Sources des données : MEDLINE, EMBASE, BIOSIS, et CENTRAL de leurs dates de création à novembre 2015.

Sélection des études : Les études sur les patients adultes ayant subi un TCC modéré ou grave et soumis à une IRM cérébrale dans la phase aiguë de soins. Les issues principales évaluées étaient la mortalité et l'échelle de devenir de Glasgow (« Glasgow Outcome Score », GOS).

Extraction des données : La sélection des études et l'extraction des données ont été effectuées indépendamment par deux auteurs. Nous avons calculé les risques relatifs (RR) avec un modèle à effets aléatoires, évalué le risque de biais à l'aide d'une version modifiée de l'outil « Quality in Prognostic Studies », et déterminé le niveau de preuve avec la méthode de « Grading of Recommendations, Assessment, Development, and Evaluation ».

Résultats : Nous avons inclus 58 études parmi lesquelles 27 (n = 1,652) ont contribué à la méta-analyse. La présence des lésions au tronc cérébral était associée avec la mortalité toutes causes confondues (RR, 1.78; 95% IC, 1.01–3.15; I_2 = 43%) ainsi qu'à une évolution défavorable (RR, 2.49; 95% IC, 1.72–3.58; I_2 = 81%) à 6 mois et plus. La présence de lésions de type axonales diffuses était associée à un risque significativement plus élevé de GOS défavorable (RR, 2.46; 95% IC, 1.06–5.69; I_2 = 74%). Le niveau de gravité identifié à l'IRM sur une échelle basée sur la profondeur des lésions cérébrales montrait que le risque de GOS défavorable augmentait avec la quantité de structures caudales atteintes. La plupart des études présentaient un risque élevé de biais méthodologique.

Conclusions : Suite à un TCC, l'IRM fournit des informations pronostiques importantes, les types de lésions cérébrales étant significativement associés à la survie à long terme et au pronostic neurologique. Compte tenu du risque élevé de biais des études sur ce sujet, des études d'envergure et bien exécutées sont nécessaires pour mieux quantifier le rôle pronostique de l'IRM aiguë effectuée suite à un TCC modéré ou grave.

2.2 Abstract

Objectives: Traumatic brain injury is a major cause of death and disability, yet many predictors of outcome are not precise enough to guide initial clinical decision-making. Although increasingly used in the early phase following traumatic brain injury, the prognostic utility of MRI remains uncertain. We thus undertook a systematic review and meta-analysis of studies evaluating the predictive value of acute MRI lesion patterns for discriminating clinical outcome in traumatic brain injury.

Data Sources: MEDLINE, EMBASE, BIOSIS, and CENTRAL from inception to November 2015.

Study Selection: Studies of adults who had MRI in the acute phase following moderate or severe traumatic brain injury. Our primary outcomes were all-cause mortality and the Glasgow Outcome Scale.

Data Extraction: Two authors independently performed study selection and data extraction. We calculated pooled effect estimates with a random effects model, evaluated the risk of bias using a modified version of Quality in Prognostic Studies and determined the strength of evidence with the Grading of Recommendations, Assessment, Development, and Evaluation.

Data Synthesis: We included 58 eligible studies, of which 27 (n = 1,652) contributed data to meta-analysis. Brainstem lesions were associated with all-cause mortality (risk ratio, 1.78; 95% CI, 1.01–3.15; I^2 = 43%) and unfavorable Glasgow Outcome Scale (risk ratio, 2.49; 95% CI, 1.72–3.58; I^2 = 81%) at greater than or equal to 6 months. Diffuse axonal injury patterns were associated with an increased risk of unfavorable Glasgow Outcome Scale (risk ratio, 2.46; 95% CI, 1.06–5.69; I^2 = 74%). MRI scores based on lesion depth demonstrated increasing risk of unfavorable neurologic outcome as more caudal structures were affected. Most studies were at high risk of methodological bias.

Conclusions: MRI following traumatic brain injury yields important prognostic information, with several lesion patterns significantly associated with long-term survival and neurologic outcome. Given the high risk of bias in the current body of literature, large well-controlled studies are necessary to better quantify the prognostic role of early MRI in moderate and severe traumatic brain injury.

2.3 Introduction

Traumatic brain injury (TBI) is the primary cause of mortality in North Americans under the age of 45 (1). Among survivors, nearly half of those with moderate or severe TBI suffer long-term disability (2), representing more than 1% of the general population in the United States (3). Early assessment of prognosis plays a fundamental role in clinical decision-making and permits counselling of patients and their families (4, 5). However, few independent predictors of outcome have been established (6), and existing risk prediction models are limited in their clinical utility (7).

In animal models, the depth of traumatic brain lesions directly relates to the severity of traumatic insults (8). Lesion depth also correlates with mortality and duration of coma in postmortem neurohistologic studies in humans (9, 10). This evidence has given rise to the "centripetal model" of TBI, where the grade of injury is determined by the most caudal cerebral structure afflicted by shearing injury (10).

Applying this model in vivo to prognosticate TBI is challenging. Although nearly all patients with TBI undergo CT, this modality lacks sensitivity for detecting deep cerebral lesions, in part due to image artefacts in the posterior fossa. MRI is being increasingly employed and has been found to be superior for detecting nonhemorrhagic intraparenchymal lesions, brain stem lesions, and shear injury considered to represent diffuse axonal injury (DAI) (11, 12). Studies indicate that CT may miss up to 30% of abnormalities detected by MRI (13); however, the prognostic significance of these lesions is uncertain.

Although numerous studies have investigated the predictive ability of various acute phase MRI lesions, considerable equipoise persists in the role of MRI for predicting long-term clinical outcome in TBI. We undertook a systematic review to evaluate the prognostic value of MRI following moderate and severe TBI by determining which lesion patterns, if any, correlated with all-cause mortality and neurologic outcome. We further sought to evaluate the methodological quality of the prognostic studies in this domain and investigate sources of clinical heterogeneity to inform the design of future studies.

2.4 Methods

2.4.1 Design

We conducted a prognostic systematic review and meta- analysis of studies relating acute MRI lesions to clinical outcomes in TBI in accordance with our published protocol (14) (PROSPERO CRD42015017074). Our design adheres to the recommendations outlined in the "Cochrane Handbook for Systematic Reviews and Meta-Analysis" (15) and the emerging body of methodology on prognostic systematic reviews (16–19), with reporting based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (20, 21).

2.4.2 Search Strategy

We systematically searched MEDLINE, EMBASE, BIOSIS, and Cochrane CENTRAL from their inception dates to November 2015. In collaboration with an information specialist, we developed search strategies specific to each database comprised of broad keywords and indexing terms combined with validated high-sensitivity filters for prognostic studies (for full MEDLINE strategy, see Appendix 1, Supplemental Digital Content 1, http:// links.lww.com/CCM/C871) (22, 23). Citations were managed with Endnote (version X7.5, Thomson Reuters, Toronto, Canada).

2.4.3 Study Selection and Eligibility Criteria

Following removal of duplicates, two reviewers (H.H., M.L.) independently undertook screening of titles and abstracts, followed by full-text review of retained articles. Discrepancies were resolved by consensus with a third author (A.F.T.).

We included cohort studies that investigated the prognostic value of structural MRI undertaken in the acute phase (≤ 28 d) of moderate or severe TBI (≥ 50% of participants with initial Glasgow Coma Scores [GCS] ≤ 12). We restricted inclusion to studies with an adult population reporting at least one of our primary outcomes of interest: mortality, Glasgow Outcome Scale (GOS), or extended GOS (GOSe). No restriction was placed on duration of follow-up, publication date, or publication language. Translators were consulted for articles published in languages other than English or French.

2.4.4 Data Extraction

Two reviewers (H.H., V.D.) independently collected study-level data using a standardized and piloted form. Discrepancies were resolved through consensus with a third reviewer (A.F.T.). We extracted information relating to study design and funding, patient demographics, clinical scores, CT findings, therapeutic and supportive measures, MRI technical characteristics, and measures of outcome presented relative to MRI findings such as lesion localization, lesion type (focal or diffuse), lesion size, and radiologic scores. When available, data stratified by TBI severity and image sequence were extracted.

Our primary outcomes were all-cause mortality and unfavorable GOS or GOSe (24). When the GOS or GOSe was dichotomized by the authors, their original definitions of unfavorable neurologic outcome were retained. If data were provided for the entire spectrum of the scores, we dichotomized the scores to define unfavorable neurologic outcome as GOS 1–3 and GOSe 1–4. Secondary outcomes included hospital and ICU length of stay, coma duration, and any clinical scales reporting patient function or outcome. In cases where patient outcome was assessed at multiple time points, we abstracted data separately for each time point.

In instances where the same study was published more than once, either the most complete article was retained or data from all articles were combined and presented as a single study in the analyses.

2.4.5 Assessment of Risk of Bias and Strength of Evidence

We evaluated methodological quality with a modified version of the Quality in Prognostic Studies tool (17), a validated method for assessing risk of bias in prognostic factor studies designed for use in prognostic systematic reviews. To increase rigor, our team further supplemented its list of searching questions with additional items from the Quality Assessment of Diagnostic Accuracy Studies-2 tool (25), creating a 26-item checklist (Appendix 2, Supplemental Digital Content 2, http://links.lww.com/CCM/C872). Studies were deemed to have adequately controlled for potential confounding if established strong independent prognostic variables (age, GCS, and pupillary reactivity) (6) were appropriately accounted for in their statistical analyses.

The strength of evidence for our primary outcomes was assessed by the modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for prognostic studies (18, 19) to determine the level of confidence in the pooled effect measures and provide an assessment of overall external validity. The quality of evidence was classified as high, moderate, low, or very low for each major association of lesion pattern and primary outcome measure.

2.4.6 Statistical Analysis and Data Synthesis

We reported categorical variables using proportions and continuous variables using means with SDs or medians with ranges. We performed meta-analysis with random effects models. Pooled dichotomous outcomes are presented as Mantel-Haenszel risk ratios (RRs) with 95% CIs. Meta-analysis for mortality and GOS outcome data was performed at all available time points in addition to global pooling at the measurement furthest from injury.

Ordinal data are presented in tabular format for each individual study as RR accompanied by 95% CI, with the lowest lesion grade taken as the reference category. Data from radiologic scores were also dichotomized according to the presence or absence of brainstem lesions and pooled using the meta-analytic technique presented above.

Between-study heterogeneity was evaluated with the I^2 statistic, and publication bias was evaluated by visual inspection of funnel plots for primary outcomes (15).

Subgroup and sensitivity analyses based on a priori specified hypotheses were undertaken to explore potential sources of heterogeneity. These analyses were based on clinical (TBI severity, lesion localization, lesion laterality, timing of outcome assessment, timing of MRI, MRI field strength, MRI sequence) and

methodological (adequate control for confounding, study risk of bias) characteristics. Analyses were performed for each lesion pattern when possible, dependant on the number of included studies and availability of outcome measures.

A two-tailed alpha of 0.05 was used for all tests and CIs. All analyses were performed with Review Manager (Version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

2.5 Results

Our search strategy yielded 26,932 unique citations. A total of 67 articles representing 58 unique studies (n = 3,306 patients) met eligibility criteria and were included in our systematic review (Fig. 1). All studies contributed to demographic data (Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/CCM/C873). Fifty-five studies contributed to outcome data, and 27 (n = 1,652 patients) subsequently underwent meta-analysis.

All included studies were observational cohorts with sample sizes ranging from 10 to 167 participants. Mean age was 34.4 (± 5.8) years, and males represented 75% of all subjects. Mortality, GOS, and GOSe outcomes were reported in 47 (81%), 37 (64%) and 10 (17%) studies, respectively. Outcome measurement was most frequently performed at 6 months but ranged from time of hospital discharge to 51 months. At the end of follow-up, overall mortality was 18.1%, and 41.5% of participants had an unfavorable neurologic outcome (Supplemental Table 1, Supplemental Digital Content 3, http:// links.lww.com/CCM/C873).

MRI was performed at a mean of 9.7 days post-TBI. The majority (n = 34) of studies employed MRI scanners with 1.5 Tesla (T) magnetic fields; eight had high-power (3.0 T) magnetic fields, and eight had magnetic fields inferior to 1.5 T. Four sequences were included in approximately half or more of the imaging protocols: T1-weighted (T1) (86% of studies), T2-weighted (T2) (76%), T2 gradient echo (T2*-GRE) (45%), and Fluid Attenuated Inversion Recovery (49%). Other imaging sequences were employed less commonly; MRI protocols for head trauma generally varied greatly (Supplemental Table 2, Supplemental Digital Content 4, http://links.lww.com/CCM/C874).

Three studies (26–34) were attributed an overall low risk of bias. Forty-six studies (12, 35–82) were at high risk of bias (Supplemental Fig. 1, Supplemental Digital Content 5, http:// links.lww.com/CCM/C875; legend, Supplemental Digital Content 15, http://links.lww.com/CCM/C885) with significant methodological concerns primarily driven by inadequate control for confounding (n = 37) and lack of consecutive patient enrollment (n = 21).

The presence of one or more brainstem lesions on MRI significantly increased the risk of all-cause mortality (five studies; n = 428 patients; RR, 1.78: 95% CI, 1.01–3.15; I_2 = 43%) (Fig. 2) and unfavorable GOS (12 studies; n = 775 patients; RR, 2.49; 95% CI 1.72–3.58; I_2 = 81%) (Fig. 3). Subgroup analysis of studies including only patients with severe TBI (GCS ≤ 8) yielded similar results to those including both moderate and severe TBI (GCS ≤ 12) (six studies; n = 289 patients; RR, 1.94 for unfavorable GOS; 95% CI, 1.38–2.73; I_2 = 63%) (Supplemental Fig. 2, Supplemental Digital Content 6, http:// links.lww.com/CCM/C876; legend, Supplemental Digital Content 15, http://links.lww.com/CCM/C885) (p = 0.20 for subgroup difference). Meta-analysis of data on the impact of brainstem lesions on GOS exhibited considerable statistical heterogeneity; however, this was reduced when assessing the brain stem with respect to its anatomical subdivisions (midbrain, pons, and medulla). Although statistically significant relationships with long-term GOS were maintained in the midbrain and pons, this was not the case in the medulla, possibly due to inadequate power or fewer patients with such lesions surviving to the time of MRI (Supplemental Fig. 3, A–C, Supplemental Digital Content 7, http://links.lww.com/ CCM/C877; legend, Supplemental Digital Content 15, http:// links.lww.com/CCM/C885).

Lesions in the corpus callosum were not found to be associated with long-term GOS (eight studies; n = 590 patients; RR, 1.28; 95% CI, 0.71–2.30; I_2 = 77%) (Supplemental Fig. 4, Supplemental Digital Content 8, http://links.lww.com/CCM/C878; legend, Supplemental Digital Content 15, http://links.lww.com/CCM/ C885). Data on the effect of lesions localized at other regions of the brain such as the cortex, the lobar white matter, the thalamus, the basal ganglia, and the cerebellum were also systematically extracted but were too sparse to be pooled for meta-analysis.

Focal cerebral lesions, including cerebral contusions and extra- axial hemorrhages, did not demonstrate significant relationships with long-term outcome (Supplemental Table 3, Supplemental Digital Content 9, http://links.lww.com/CCM/C879). The presence of shear injury compatible with DAI was significantly associated with unfavorable GOS (eight studies; n = 359 patients; RR, 2.46; 95% CI, 1.06–5.69; I_2 = 74%) (Fig. 4), but this analysis exhibited substantial heterogeneity. Subgrouping studies with a strictly severe TBI (GCS ≤ 8) population from those also including both severe and moderate TBI (GCS ≤ 12) resolved a large proportion of this heterogeneity (three studies; n = 230 patients; RR, 4.23; 95% CI, 1.40–12.80; I_2 = 35%) (Fig. 4) with no statistically significant difference between the two subgroups (p = 0.10). The remaining het- erogeneity was further resolved in sensitivity analyses examining only studies employing either susceptibility weighted imaging or T2*-GRE sequences sensitive for the detection of shear injury patterns, with both sub- groups of GCS severity demonstrating statistically significant associations with unfavorable GOS (Supplemental Fig. 5, Supplemental Digital Content 10, http://links.lww.com/CCM/C880; legend, Supplemental Digital Content 15, http://links.lww.com/CCM/C885).

Four studies (43, 45, 58, 61) graded brain lesions on MRI using a radiologic score initially developed by Firsching et al (43). Three studies (12, 26, 28, 29) employed the Adams-Gentry score (83), a radiologically adapted method of classifying histologic brain lesions (10). The staging assigned by both scores is determined by the most caudal brain lesion present, though their definitions vary (Table 1). Pooled data from both scores demonstrate progressively increasing risks of unfavorable neurologic outcome as maximal depth of lesion increases (Table 1). To increase comparability, the scores were dichotomized to distinguish between stages of nonbrainstem lesions (Firsching grade I, Adams-Gentry stages 1 and 2) versus stages where some form of brainstem lesion is present (Firsching grades II to IV, Adams- Gentry stage 3). Data from the seven studies in binary form were deemed adequately homogenous to be pooled overall, and standard meta-analysis was undertaken for the outcome of unfavorable GOS. Pooled data from the seven studies entering this analysis (n = 530 patients) demonstrate a statistically significant relationship between classification in a stage representing brainstem injury and unfavorable GOS (RR, 2.71; 95% CI, 1.91–3.85; I^2 = 64%; Supplemental Fig. 6, Supplemental Digital Content 11, http://links.lww.com/CCM/C881; legend, Supplemental Digital Content 15, http://links.lww.com/CCM/ C885). The results of this alternative meta-analysis further corroborate those of the first analysis of brainstem lesions presented above (Fig. 3), as both the direction and the force of the association are consistent.

Sensitivity analyses for the association relating brainstem lesions with unfavorable GOS based on the timing of outcome assessment (at 6 vs > 6 mo), MRI field strength (< 1.5 T vs ≥1.5 T), adequacy of control for confounding (presence of adjustment for age, GCS, and pupillary reactivity vs absence), and methodological quality (low or unclear risk of bias vs high risk of bias) all yielded consistent results without evidence of major differences between groups. The sensitivity analysis by mean timing of MRI post-TBI (≤ 7 vs > 7 d) demonstrated divergence between groups, with a higher RR of unfavorable GOS in studies where MRI was undertaken greater than 7 days following TBI (Supplemental Table 4, Supplemental Digital Content 12, http://links.lww.com/CCM/C882). For the association relating DAI type lesions with unfavorable GOS, sensitivity analysis based on the use of MRI sequences sensitive for shear injury (employing either T2*-GRE or SWI vs neither) demonstrated that only studies employing at least one of the two sequences retained a significant relationship with unfavorable GOS, although the difference between groups did not reach statistical significance (Supplemental Table 5, Supplemental Digital Content 13, http://links.lww.com/CCM/C883).

Visual evaluation of funnel plots for meta-analyses of mortality and unfavorable GOS did not suggest evidence of publication bias. Level of recommendation was determined by GRADE; the quality of evidence for the analyses correlating medullary and corpus callosum lesions with unfavorable GOS was low. The brainstem, midbrain, pons, and shear injury lesion analyses' associations with unfavorable GOS had a moderate quality of

evidence. The quality of evidence for mortality was evaluated only in relation to brainstem lesions and was low. (Supplemental Table 6, Supplemental Digital Content 14, http://links.lww.com/CCM/C884).

2.6 Discussion

We found a strong association between brainstem lesions on MRI and unfavorable long-term prognosis in patients with moderate and severe TBI. Injury to any region of the brain stem was significantly predictive of both all-cause mortality and unfavorable neurologic outcome. Classification of the depth of brain injury visualized on MRI by radiologic scores was also predictive of unfavorable outcome.

Our study is the first to quantitatively summarize the relationship between acute MRI lesion patterns and long-term clinical outcome. Corollary studies in similar domains, such as veterinary studies applying the Firsching score in dogs with TBI (84), corroborate the neuroanatomical significance of brainstem lesions on prognosis found in our systematic review.

In our study, 41.5% of patients with moderate and severe TBI progressed to unfavorable neurologic outcome (death, vegetative state or severe disability). This is consistent with previous data on the incidence of disability following TBI (2). As patients with TBI are often young with few or no comorbidities, accurate determination of prognosis is essential for guiding early therapeutic and end-of-life decisions. This was highlighted by a recent large Canadian multicenter cohort study on severe TBI (85) demonstrating considerable variation in mortality rates between centers, driven in part by variability of life-sustaining therapy withdrawal.

Our review has several strengths. We conducted this study according to an a priori published protocol, with prespecified analyses, and employed methodology designed specifically for prognostic systematic reviews, including tools for assessing risk of bias and quality of evidence validated for prognostic factor studies. Our search strategy was highly sensitive and contained search filters validated for prognostic studies. We did not place a limit on the type of MRI lesions to include in our review to gather data representative of all forms of lesions patterns reported in the TBI literature.

There are limitations to our systematic review. We encountered high levels of heterogeneity; however, a portion of this was reduced in our prespecified subgroup analyses, including analysis of the brain stem by its anatomical substructure and separation by TBI severity, as well as in sensitivity analyses of shear injury by the use of sensitive imaging sequences. Unresolved heterogeneity remained significant and may be due to other between-study factors such as differences in MRI variables, including evolving technology, magnetic field strength, diversity of imaging sequences, and either the lack or use of automated tools for image analysis which may contribute to variability in lesion measurement in the context of baseline weak associations. The term “lesion” or its synonyms were often not defined in primary studies, and it was not possible to meta-analyze data

by a specific image sequence or lesion appearance; in the case of brainstem lesions specifically, the majority of primary studies did not distinguish between primary lesions induced directly by the forces of the initial blunt traumatic insult and secondary lesions due to damage from neighboring structures, such as via injury due to cerebral herniation or laceration on the free edge of the tentorium. This is compounded by the evolving nature of lesions not captured by MRI evaluation at a single point in time. The overall prognostic information detected may therefore be the result of multiple diverse pathophysiologic processes as the available data are not adequate for establishing robust associations between specific MRI signal characteristics and underlying tissue injury. Last, although this meta-analysis was conducted according to high methodological standards, our results are limited by the quality of the studies included; most did not report data adjusted for confounding with established prognosticators and were at risk of selection bias due to frequent lack of consecutive patient recruitment.

Additional large cohort studies with adequate control of confounding are required to corroborate the findings of this meta-analysis (86). Given the diversity of underlying injury mechanisms which contribute to the overall phenotype of TBI, the function of energy delivery at the moment of trauma, its translation to MRI signal abnormalities, and the relationship of such lesion characteristics to underlying brain tissue injury remain to be fully elucidated in future investigations.

2.7 Conclusion

Early assessment of deep cerebral structures with MRI in moderate and severe TBI yields significant prognostic information. Given the low quality of evidence in the current body of literature, further studies are required to confirm our meta-analysis' findings and evaluate the independent predictive value of MRI.

2.8 Acknowledgments

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2.10 Tables

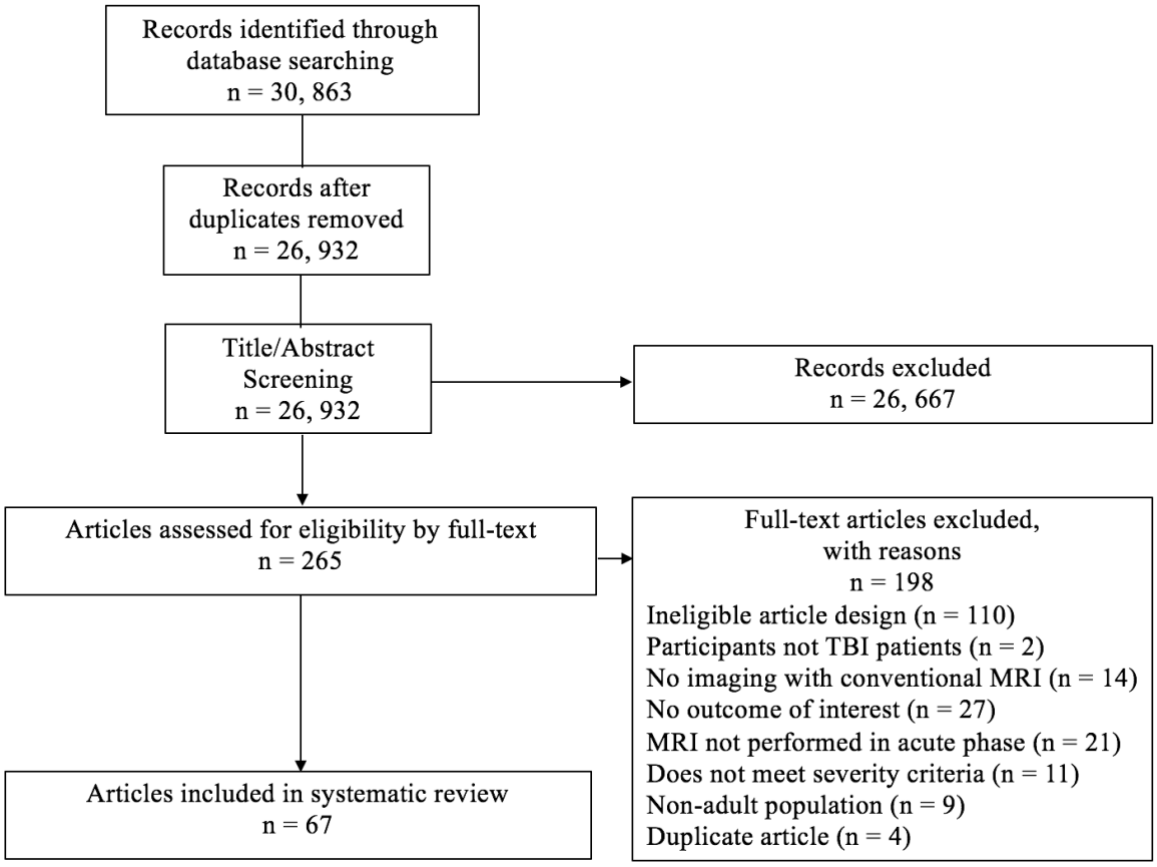
2.10.1 Table 1: Relative Risk for Unfavourable GOS in Depth-of-Lesion MRI Scores in Moderate and Severe TBI

Firsching Score (4 studies, n = 353)				
Grade	Definition	RR	95% CI	I_2
Grade I	Supratentorial lesions only	1.00	(Reference)*	N/A
Grade II	Unilateral brainstem lesions	1.64	1.21 – 2.23	0%
Grade III	Bilateral midbrain lesions	2.67	1.80 – 3.96	63%
Grade IV	Bilateral pontine lesions	2.81	1.73 – 4.56	73%
Adams-Gentry Classification (3 studies, n = 165)				
Stage	Definition	RR	95% CI	I_2
Stage 1	Lesions to the subcortical lobar white matter or cerebellum only	1.00	(Reference)*	N/A
Stage 2	Lesions attaining the corpus callosum	2.01	0.90 – 4.50	0%
Stage 3	Lesions attaining the brainstem (dorsolateral midbrain or pons)	4.57	2.23 – 9.33	0%

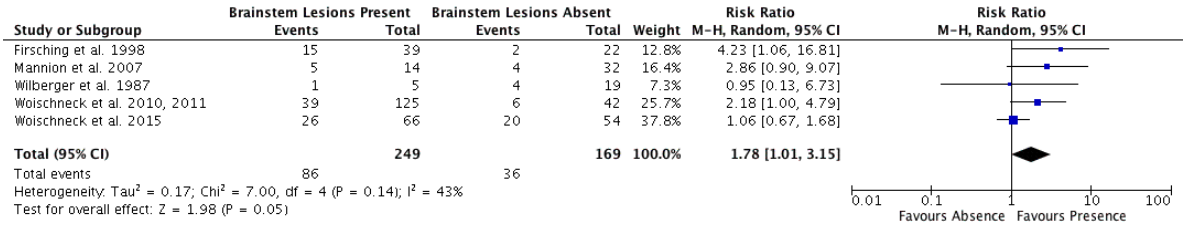
*Pooled separately by category, with the most superficial category as reference

2.11 Figures

2.11.1 Figure 1: Study Selection Flow



2.11.2 Figure 2: Relative Risk of Mortality in Moderate and Severe TBI with Brainstem Lesions on Acute MRI



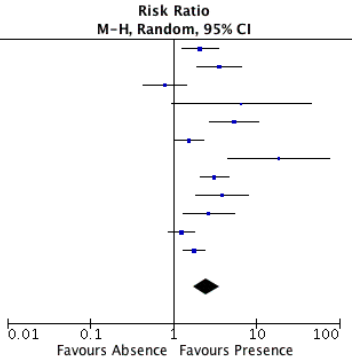
Study or Subgroup	Brainstem Lesions Present Events	Total	Brainstem Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Firsching et al. 1998	15	39	2	22	12.8%	4.23 [1.06, 16.81]
Mannion et al. 2007	5	14	4	32	16.4%	2.86 [0.90, 9.07]
Wilberger et al. 1987	1	5	4	19	7.3%	0.95 [0.13, 6.73]
Woischneck et al. 2010, 2011	39	125	6	42	25.7%	2.18 [1.00, 4.79]
Woischneck et al. 2015	26	66	20	54	37.8%	1.06 [0.67, 1.68]
Total (95% CI)		**249**		**169**	**100.0%**	**1.78 [1.01, 3.15]**
Total events	86		36			

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 7.00$, df = 4 (P = 0.14); $I^2 = 43\%$
Test for overall effect: Z = 1.98 (P = 0.05)

2.11.3 Figure 3: Relative Risk of Unfavourable GOS in Moderate and Severe TBI with Brainstem Lesions on Acute MRI

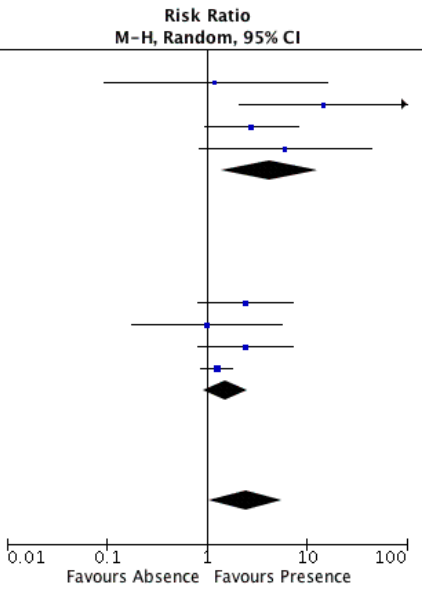
Study or Subgroup	Brainstem Lesions Present Events	Total	Brainstem Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bagley et al. 2000	5	5	10	23	9.5%	2.10 [1.25, 3.50]
Carpentier2006	11	11	7	27	8.7%	3.58 [1.92, 6.68]
Chew et al. 2012	10	21	9	15	8.8%	0.79 [0.43, 1.46]
Iwamura et al. 2012	6	10	1	11	2.7%	6.60 [0.95, 45.75]
Lagares et al. 2009	22	33	8	65	8.2%	5.42 [2.71, 10.82]
Mannion et al. 2007	11	13	18	33	10.3%	1.55 [1.05, 2.29]
Moen/Skandsen et al.	15	30	2	75	4.3%	18.75 [4.56, 77.06]
Potapov et al. 2014	58	76	21	86	10.3%	3.13 [2.11, 4.63]
Wedekind et al. 1999	24	29	6	28	8.0%	3.86 [1.86, 8.00]
Wedekind et al. 2002	10	14	7	26	8.1%	2.65 [1.30, 5.42]
Wilberger et al. 1987	5	5	14	19	10.5%	1.26 [0.88, 1.82]
Woischneck et al. 2015	54	66	25	54	10.8%	1.77 [1.30, 2.41]
Total (95% CI)		**313**		**462**	**100.0%**	**2.49 [1.72, 3.58]**
Total events	231		128			

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 57.84$, df = 11 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 4.87$ ($P < 0.00001$)



2.11.4 Figure 4: Relative risk of Unfavourable GOS in TBI with Signs of Shear Injury Compatible with Diffuse Axonal Injury on Acute MRI, by Overall and Severe GCS

Study or Subgroup	DAI Present Events	Total	DAI Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Diffuse Axonal Injury | Overall GCS						
Garnett et al. 2000	0	1	3	16	6.9%	1.21 [0.09, 15.95]
Lagares et al. 2009	29	65	1	33	9.6%	14.72 [2.10, 103.38]
Marino et al. 2006	3	3	2	7	14.8%	2.80 [0.94, 8.35]
Moen/Skandsen et al.	16	76	1	29	9.4%	6.11 [0.85, 43.98]
Subtotal (95% CI)		**145**		**85**	**40.7%**	**4.23 [1.40, 12.80]**
Total events	48		7			
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 4.64$, df = 3 ($P = 0.20$); $I^2 = 35\%$						
Test for overall effect: $Z = 2.56$ ($P = 0.01$)						
6.1.2 Diffuse Axonal Injury | Severe GCS						
Holshouser et al. 2006	6	16	4	26	14.7%	2.44 [0.81, 7.33]
Iwamura et al. 2012	6	18	1	3	10.7%	1.00 [0.18, 5.63]
Shutter et al. 2004	6	16	4	26	14.7%	2.44 [0.81, 7.33]
Wilberger et al. 1987	5	5	14	19	19.1%	1.26 [0.88, 1.82]
Subtotal (95% CI)		**55**		**74**	**59.3%**	**1.54 [0.94, 2.54]**
Total events	23		23			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.98$, df = 3 ($P = 0.26$); $I^2 = 25\%$						
Test for overall effect: $Z = 1.71$ ($P = 0.09$)						
Total (95% CI)		**200**		**159**	**100.0%**	**2.46 [1.06, 5.69]**
Total events	71		30			
Heterogeneity: $Tau^2 = 0.93$; $Chi^2 = 27.19$, df = 7 ($P = 0.0003$); $I^2 = 74\%$						
Test for overall effect: $Z = 2.11$ ($P = 0.04$)						
Test for subgroup differences: $Chi^2 = 2.66$, df = 1 ($P = 0.10$), $I^2 = 62.3\%$						



2.12 Appendix 1: MEDLINE Search

1. ((brain[TIAB] OR brains[TIAB] OR brainstem*[TIAB] OR head[TIAB] OR heads[TIAB] OR craniocerebral*[TIAB] OR intracrani*[TIAB] OR intra-crani*[TIAB] OR intercrani*[TIAB] OR inter-crani*[TIAB] OR cerebr*[TIAB] OR cerebel*[TIAB] OR forebrain*[TIAB]) AND (injury*[TIAB] OR injuries[TIAB] OR injured[TIAB] OR trauma[TIAB] OR traumas[TIAB] OR traumatic*[TIAB] OR traumato*[TIAB] OR damag*[TIAB])) OR TBI[TIAB] OR Craniocerebral Trauma[MeSH:NoExp] OR

Brain Injuries[Mesh:NoExp] OR Brain Hemorrhage, Traumatic[Mesh] OR Diffuse Axonal Injury[Mesh:NoExp] OR Coma, Post-Head Injury[Mesh:NoExp] OR Head Injuries, Closed[Mesh:NoExp] OR Intracranial Hemorrhage, Traumatic[Mesh]

2. magnetic resonanc*[TIAB] OR "diffusion weighted"[TIAB] OR "diffusion tensor"[TIAB] OR MRI[TIAB] OR MR[TIAB] OR fMRI [TIAB] OR dMRI[TIAB] OR MRS[TIAB] OR MRA[TIAB] OR DTI[TIAB] OR DWI[TIAB] OR "T1-weighted"[TIAB] OR "T1 weighted"[TIAB] OR T1WI[TIAB] OR T1[TIAB] OR T1rho[TIAB] OR "T2-weighted"[TIAB] OR "T2 weighted"[TIAB] OR T2WI[TIAB] OR T2[TIAB] OR "T2*-weighted"[TIAB] OR "T2*WI"[TIAB] OR "T2*"[TIAB] OR "T2*-Gradient Echo"[TIAB] OR "T2*-GRE"[TIAB] OR "Fluid attenuated inversion recovery"[TIAB] OR FLAIR[TIAB] OR "Susceptibility weighted"[TIAB] OR SWI[TIAB] OR

"Magnetic Resonance Imaging"[MeSH:NoExp] OR "Diffusion Magnetic Resonance Imaging"[MeSH:Exp] OR "Echo-Planar Imaging"[MeSH:NoExp] OR "Magnetic Resonance Angiography"[MeSH:NoExp] OR

"Magnetic Resonance Imaging, Interventional"[MeSH]

3. Incidence[MeSH:NoExp] OR Mortality[MeSH Terms] OR Follow Up Studies[MeSH:NoExp] OR pognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]

4. #1 AND #2 AND #3

5. animals[MeSH] NOT humans[MeSH]

6. #4 not #5

2.13 Appendix 2: Methodological Quality (Risk of Bias) Evaluation Tool for Studies of Prognostic Tests (Modified QUIPS Tool with Additions from QUADAS-2)

Domain	Description	Judgment	Risk of bias	Applicability concerns
01. Study Participation				
Was consecutive or appropriate random sampling used to enrol patients? (As opposed to voluntary sampling)	*Describe methods of patient selection* *Describe included patients (previous testing, presentation, intended use of index test, and setting)*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was there adequate participation in the study by eligible individuals?	Low risk if: - Majority (≥85%) of individuals meeting eligibility criteria participated in study	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was a case-control design avoided?	Low risk if: - Consecutive or random selection *Careful in distinguishing bias vs. applicability concerns: judgement call	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Did the study avoid inappropriate exclusions?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the included patients do not match the review question?	- All adult (no paediatric) population - Moderate or severe - All pathologies are TBI - Blunt head injury (no penetrative)	□ Adults □ Moderate or severe □ Blunt TBI		
Overall	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between the prognostic factor and outcome	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
02. Prognostic Factor Measurement				
Blinding Were the prognostic marker results interpreted without knowledge of clinical data?	*Describe the prognostic marker and how it was conducted and interpreted*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Was the method of prognostic factor measurement adequately valid to and reliable to limit misclassification bias?	Low risk if: - Method of measurement recognized as valid or standard of practice in the domain - Information on reliability/validity of method of measurement presented (ex. Cohen's kappa, etc.) - Diagnostic criteria presented	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Inter-rater agreement Was inter-rater agreement evaluated via a statistical measure (ex. Cohen's kappa)?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	

If a threshold was used, was it specified *a priori*? [□ Not applicable]		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were diagnostic criteria for prognostic factors well-defined?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the prognostic marker, its conduct, or its interpretation differ from the review question? (including timing of assessment)	Low risk if: - The method and setting of measurement of the prognostic factor is the same for all participants Applicability concern if: - Prognostic marker not associated to specific sequence (applicability issue; bias unlikely to be affected) - Prognostic marker (MRI) measured over very long period	□ Specific sequence □ Measured at specific time or over a short time window	□ High □ Low □ Unclear	
Overall	The prognostic factor is adequately measured in study participants to sufficiently limit potential bias.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
03. Outcome Measurement				
Was the outcome measurement adequate (evaluated reliably and validly)?	*Describe the outcome measurement and how it was conducted and interpreted*	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all patient outcomes evaluated identically? (method/setting standardized)	Low risk if: - Data on reliability/validity - Similar method of evaluation for all subjects - Outcome evaluator blinded to patient history	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Blinding Were the outcome results interpreted without knowledge of the results of the prognostic markers?		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are there concerns that the prognostic marker, its conduct, or its interpretation differ from the review question? (including timing of assessment)	Applicability concern if: - Outcome measure reported as a binomial variable with a cut-off different from our review - Outcome is measured or timing reported over very long intervals - Minimum 1 measure of outcome at ≥6 months post-TBI	□ Same cut-off □ Specific timing of assessment or short time window □ Minimum of 1 measure at ≥6 months post-TBI		
Overall	The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear

04. Study Attrition				
Was the response rate (proportion of baseline sample completing the study and providing outcome data) adequate? Are there subjects not included in the analysis?	Low risk if: - < 15% lost to follow-up - Loss to follow-up but with multiple imputation method - Intent-to-treat analysis	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all subjects included in the analysis? (Loss to follow-up? Withdrawal? Subjects not tested? Missing data? Etc.)		□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were attempts made to collect information on participants who dropped out or were lost to follow-up?	Reasonable attempts were made by investigators to acquire information on participants who did not complete the study and characterize them	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Are baseline characteristics and outcomes similar in patients who completed the study compared to those who did not?	Low risk if: No important differences between participants having completed the study and those who did not	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The loss to follow-up or missing data affects a small proportion of the study participants and is not associated with key characteristics sufficient to limit potential bias to the observed relationship between the prognostic factor and outcome	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
05. Timing				
Was there an appropriate interval between the prognostic marker and the outcome measurement? (Biologically plausible, sufficient duration for outcome to occur)	*Describe the interval between prognostic markers and the outcome measurement* Low risk if: - Mortality or GOS measured at hospital discharge or later	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The interval of time between measurements of the prognostic factor and outcome is adequate to respond to the study hypothesis	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
06. Study Confounding				
Did the study adequately control for potential confounders?	*Describe any method used to control for potential confounding* Low if: - Adjustment for: age, motor subscale of the GCS or GCS, and pupillary reactivity	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	

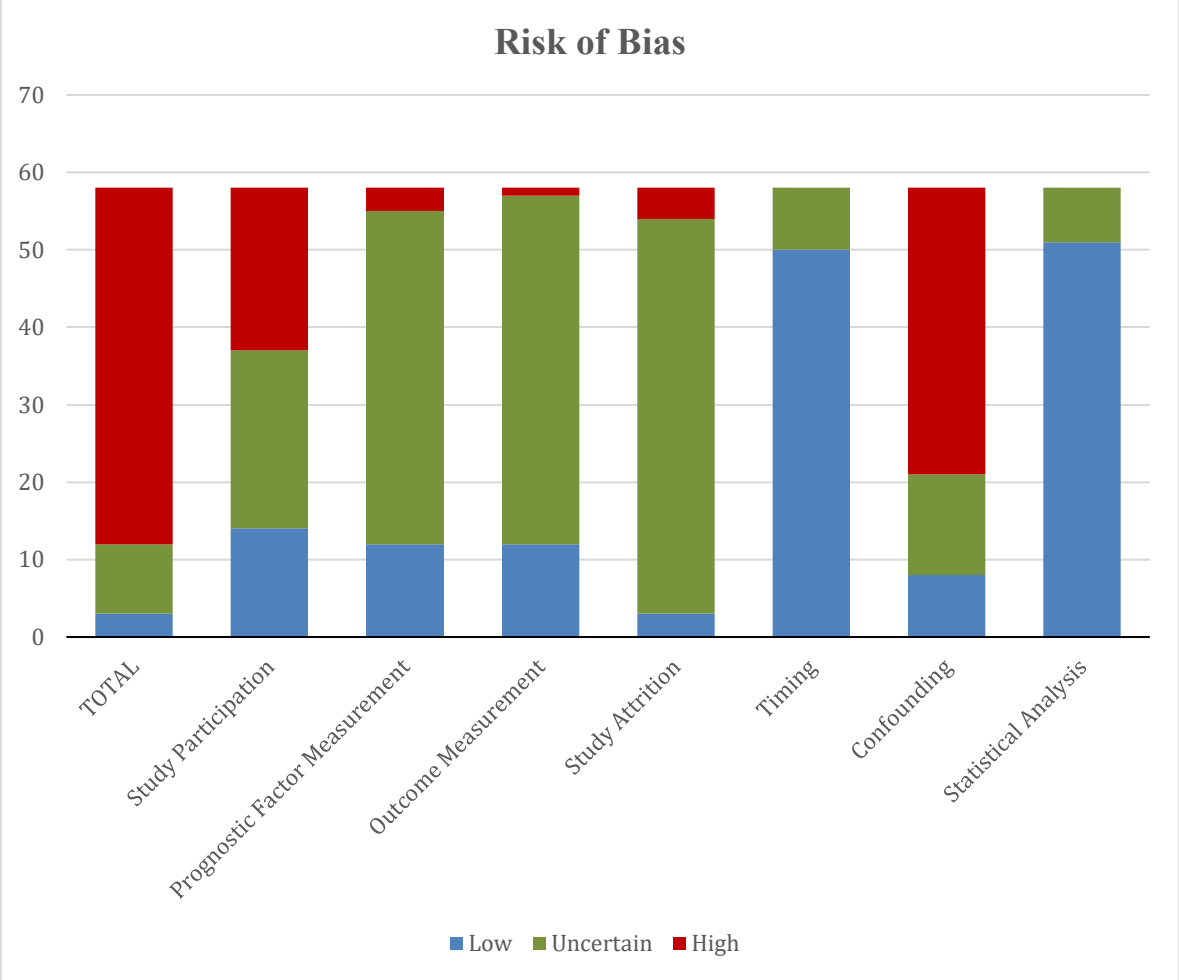
Are important potential confounders accounted for in the analysis?	High if: - No adjusted measure reported - Inadequate adjustment (important variables not taken into account, improper statistical method used)			
Are the measurements of all important confounders adequately valid and reliable?	Method of measurement recognized as valid or standard of practice in the domain The method and setting of confounding measurement are the same for all study participants	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between the prognostic factor and outcome.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear
07. Statistical Analysis				
Are the statistical methods employed in the study adequate?	The statistical tests/methods are appropriate for the type of data analysed and are adequate for testing the study hypothesis	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Is the model development strategy adequate (if applicable)?	The strategy for model building is appropriate and is based on a conceptual framework or model The selected statistical model is adequate for the design of the study.	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Were all statistical analyses pre-specified?	Low if: - No post-hoc data analysis Reviewer's judgement if: - Post-hoc analysis clearly identified as such and adequately justified in discussion	□ Yes □ No □ Unclear	□ High □ Low □ Unclear	
Overall	The statistical analysis is appropriate for the design and hypothesis of the study, limiting potential for invalid or spurious results.	□ True □ False □ Unclear	□ High □ Low □ Unclear	□ High □ Low □ Unclear

Modified from:

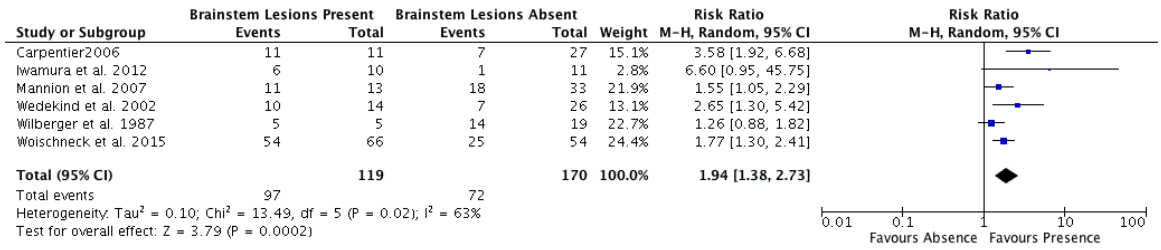
- Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine*. 2013;158(4):280-6.
- Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*. 2011;155(8):529-36

2.14 Appendix 3: Supplementary Figures

2.14.1 Supplementary Figure 1: Risk of Bias Assessment (adapted QUIPS Tool)



2.14.2 Supplementary Figure 2: Relative Risk of Unfavourable GOS in Severe TBI with Brainstem Lesions on Acute MRI



Study or Subgroup	Brainstem Lesions Present Events	Total	Brainstem Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Carpentier2006	11	11	7	27	15.1%	3.58 [1.92, 6.68]
Iwamura et al. 2012	6	10	1	11	2.8%	6.60 [0.95, 45.75]
Mannion et al. 2007	11	13	18	33	21.9%	1.55 [1.05, 2.29]
Wedekind et al. 2002	10	14	7	26	13.1%	2.65 [1.30, 5.42]
Wilberger et al. 1987	5	5	14	19	22.7%	1.26 [0.88, 1.82]
Woischneck et al. 2015	54	66	25	54	24.4%	1.77 [1.30, 2.41]
Total (95% CI)		**119**		**170**	**100.0%**	**1.94 [1.38, 2.73]**
Total events	97		72			

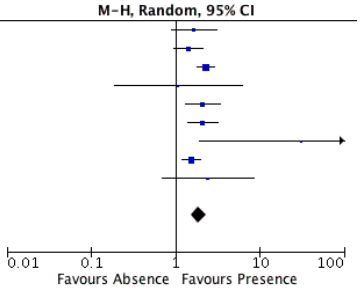
Heterogeneity: Tau² = 0.10; Chi² = 13.49, df = 5 (P = 0.02); I² = 63%
Test for overall effect: Z = 3.79 (P = 0.0002)

2.14.3 Supplementary Figure 3: Relative Risk of Unfavourable GOS in Moderate and Severe TBI with Brainstem Lesions on Acute MRI, by Lesion Depth Within the Brainstem

A. Midbrain

Study or Subgroup	Midbrain Lesions Present Events	Total	Midbrain Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bagley et al. 2000	2	2	13	26	8.3%	1.67 [0.89, 3.13]
Mannion et al. 2007	9	11	20	35	15.1%	1.43 [0.96, 2.14]
Potapov et al. 2014	27	30	52	132	23.2%	2.28 [1.79, 2.91]
Shibata et al. 2000	5	14	1	3	1.4%	1.07 [0.19, 6.15]
Wedekind et al. 1999	16	20	14	37	12.6%	2.11 [1.32, 3.37]
Weiss et al. 2008	25	31	16	42	14.2%	2.12 [1.39, 3.23]
Woischneck et al. 2008	21	85	0	62	0.6%	31.50 [1.94, 510.27]
Woischneck et al. 2015	44	54	35	66	22.2%	1.54 [1.18, 1.99]
Yu et al. 2012	6	19	3	23	2.6%	2.42 [0.70, 8.41]
Total (95% CI)		**266**		**426**	**100.0%**	**1.87 [1.52, 2.31]**
Total events	155		154			

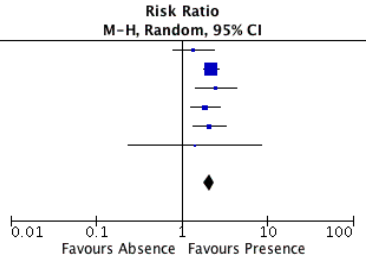
Heterogeneity: Tau² = 0.03; Chi² = 13.20, df = 8 (P = 0.11); I² = 39%
Test for overall effect: Z = 5.87 (P < 0.00001)



B. Pons

Study or Subgroup	Pontine Lesions Present Events	Total	Pontine Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mannion et al. 2007	2	2	27	44	7.6%	1.36 [0.78, 2.38]
Potapov et al. 2014	15	15	64	147	56.9%	2.22 [1.81, 2.72]
Shibata et al. 1999	5	5	9	25	7.5%	2.51 [1.43, 4.40]
Wedekind et al. 1999	7	8	23	49	15.0%	1.86 [1.25, 2.77]
Weiss et al. 2008	26	33	15	40	12.3%	2.10 [1.36, 3.25]
Woischneck et al. 2008	1	5	20	142	0.7%	1.42 [0.23, 8.59]
Total (95% CI)		**68**		**447**	**100.0%**	**2.08 [1.79, 2.43]**
Total events	56		158			

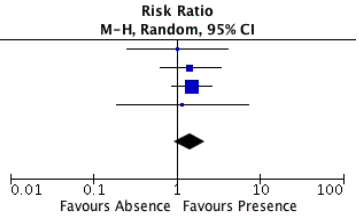
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 5 (P = 0.62); I² = 0%
Test for overall effect: Z = 9.38 (P < 0.00001)



C. Medulla

Study or Subgroup	Medullary Lesions Present Events	Total	Medullary Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Potapov et al. 2014	1	2	78	160	9.2%	1.03 [0.25, 4.14]
Wedekind et al. 1999	1	1	29	56	25.6%	1.45 [0.63, 3.35]
Weiss et al. 2008	2	2	39	71	59.9%	1.52 [0.88, 2.63]
Woischneck et al. 2008	1	6	20	141	5.3%	1.18 [0.19, 7.36]
Total (95% CI)		**11**		**428**	**100.0%**	**1.43 [0.93, 2.18]**
Total events	5		166			

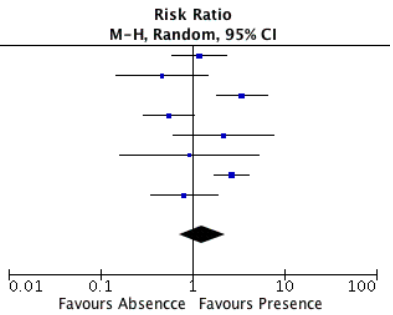
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)



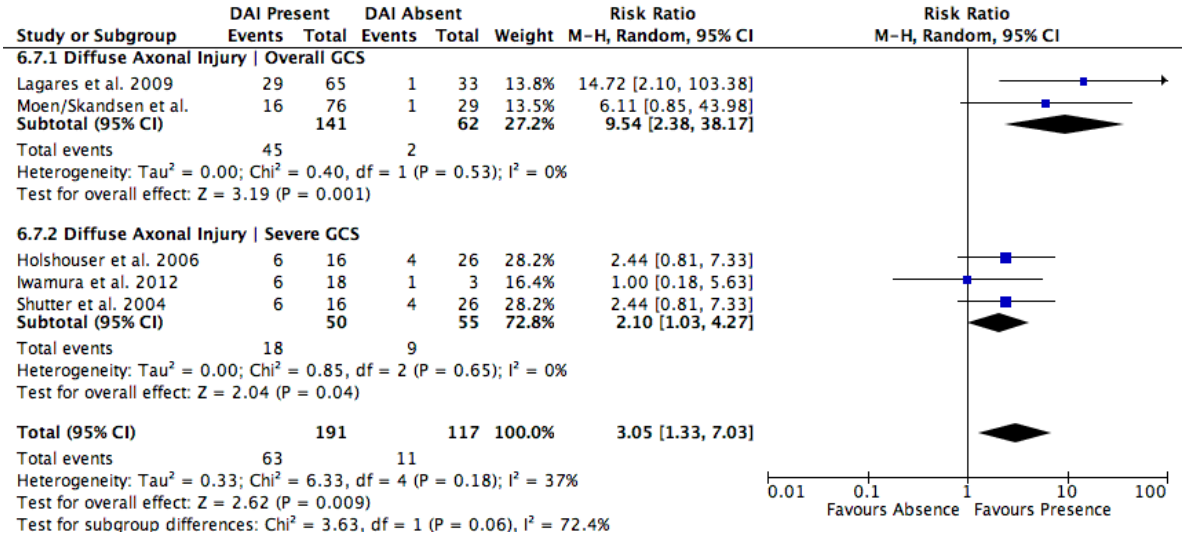
2.14.4 Supplementary Figure 4: Relative Risk of Unfavourable GOS in TBI with Corpus Callosum Lesions on Acute MRI

Study or Subgroup	CC Lesions Present Events	Total	CC Lesions Absent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bagley et al. 2000	6	10	9	18	14.3%	1.20 [0.60, 2.38]
Hilario et al. 2012	2	6	32	45	10.6%	0.47 [0.15, 1.48]
Lagares et al. 2009	20	36	10	62	14.7%	3.44 [1.82, 6.52]
Potapov et al. 2014	7	24	72	138	14.6%	0.56 [0.29, 1.06]
Shibata et al. 1999	12	22	2	8	9.8%	2.18 [0.62, 7.69]
Shibata et al. 2000	1	3	5	14	6.9%	0.93 [0.16, 5.36]
Wedekind et al. 1999	16	17	14	40	16.2%	2.69 [1.73, 4.17]
Woischneck et al. 2008	7	56	14	91	13.0%	0.81 [0.35, 1.89]
Total (95% CI)		**174**		**416**	**100.0%**	**1.28 [0.71, 2.30]**
Total events	71		158			

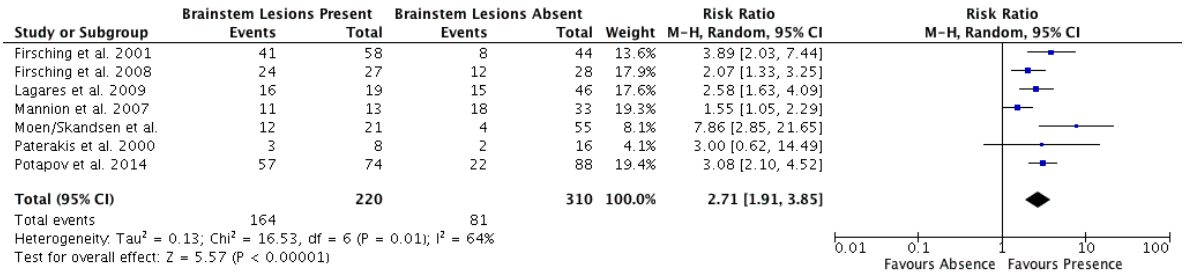
Heterogeneity: Tau² = 0.51; Chi² = 30.85, df = 7 (P < 0.0001); I² = 77%
Test for overall effect: Z = 0.82 (P = 0.41)



2.14.5 Supplementary Figure 5: Relative Risk of Unfavourable GOS in TBI with Signs of Shear Injury Compatible with Diffuse Axonal Injury on Acute MRI Employing Either Susceptibility Weighted Imaging or T2* Gradient Echo Sequences, by Overall and Severe GCS



2.14.6 Supplementary Figure 6: Relative Risk for Unfavourable GOS with Firsching Grades II to IV or Adams-Gentry Stage 3 on Acute MRI in TBI



2.15 Appendix 4: Supplementary Tables

2.15.1 Supplementary Table 1: Demographic Characteristics of Included Studies

Study (year)	Number of subjects	Age (years); mean ± SD (range)	Male/Female Ratio	Initial GCS; mean ± SD (Range)	Timing of outcome assessment (months); Mean ± SD (Range)	Type of Outcome Measure	Unfavourable GOS [latest]; n (%)
Bagley et al. (2000)	28	36.2 ± 17.5 (19-77)	17/11	8.4 ± 4	(3-36)	GOS	15 (54%)
Bavetta et al. (1994)	10	29.4 (17-60)	8/2	NR	17 (12-24)	GOSe	3 (30%)
Betz et al. (2012)	41	38 ± 17	33/8	NR	Median = 0.6 (0.13-1.6)	Mortality	NR
Carpentier et al. (2006)	40	33 ± 15	NR	6 ± 3	18	GOS	18 (45%)
Chastain et al. (2009)	38	35.7	30/8	7.8 ± 4.1 (3-15)	9.2 (0.1-22)	GOS	10 (26%)
Chelly et al. (2011)	124	28 ± 15.8	100/24	6.6 ± 2.5	12.3 ± 10.9 (3-51)	GOS	64 (52%)
Chew et al. (2012)	36	45.5 (17-90)	25/11	6 (3-15)	6	GOS	19 (53%)
de la Plata et al. (2007)	24	28.2 ±13·3	16/8	5.1 ± 4.2 (3-15)	6	GOSe	11 (46%)
Ding et al. (2008)	20	26 ± 12 (16-62)	13/7	7 ± 5 (3-15)	Median = 8 (6-11)	Other	NR
Du et al. (2011)	72	41.3 (17-66)	54/18	NR	3	GOSe	26 (36%)

Firsching et al. (1998)	61	23 (7-65)	38/23	NR	NR	Mortality	NR
Firsching et al. (2001)	102	36 (2-86)	76/26	NR	22 (3-36)	GOS	49 (48%)
Firsching et al. (2002)	100	31 (4-86)	64/36	NR	6	Mortality	NR
Firsching et al. (2008)	55	38.7	42/13	NR	6	GOS	36 (65%)
Galanaud et al. (2012)	105	36.8 ± 16	85/20	5.2 (3-8)	12	GOS	40 (38%)
Garnett et al. (2000)	17	37	15/2	11.4	6	GOS	3 (18%)
Gerber et al. (2004)	43	32 (17-59)	31/12	NR	12	Other	NR
Godersky et al. (1990)	49	29 (14-74)	40/9	9 (4-15)	NR	Other	NR
Hilario et al. (2012)	52	26	38/14	NR	6	GOSe	17 (33%)
Holshouser et al. (2006)	42	30 ± 16 (14-79)	28/14	5 ± 2 (3-8)	1, 3, 6-12	GOS	10 (24%)
Hou et al. (2007)	37	30 ± 16.8	28/9	NR	6-12	GOS	10 (27%)
Iwamura et al. (2012)	21	34 (8-77)	16/5	5.3 (3-8)	6	GOS	7 (33%)
Janousek et al. (1999)	42	38 (8-88)	29/13	NR	2-50	Mortality	NR
Kuchta et al. (2009)	44	31 (15-64)	NR	NR	6	Mortality	NR

Lagares et al. (2009)	100	33 (15-71)	83/17	NR	6	GOSe	30 (30%)
Ledig et al. (2015)	61	38.6 ± 14.9	48/13	5	6	GOS	27 (44%)
Lutkenhoff et al. (2013)	24	35.6 ± 15.3	21/3	NR	6	GOSe	15 (63%)
Lv et al. (2010)	87	41.3 ± 18	72/15	6.0 ± 1.5	12	GOS	43 (49%)
Mannion et al. (2007)	46	34 (16-70)	35/11	NR	6	GOS	29 (63%)
Marino et al. (2006)	10	44.6 (21-77)	7/3	NR	3	GOS	5 (50%)
Moen/Skandsen et al. (2010-2012, 2014)	128	33.9 (11.4-69.3)	96/32	Median = 8 (3-15)	12	GOSe	22 (17%)
Paterakis et al. (2000)	24	(15-64)	21/3	NR	6	GOS	5 (21%)
Perez et al. (2014)	16	29.1 ± 11.3	14/2	6.8 ± 4.6	7	GOSe	NR
Potapov et al. (2014)	162	29.6 ± 12.8 (8-72)	109/53	8 ± 3	NR	GOS	79 (49%)
Prieto-Valderrey et al. (2013)	23	37.0 ± 18.8	15/8	NR	ICU discharge, 6	GOS	10 (43%)
Reissberg et al. (2003)	100	37.5 (2-80)	78/22	NR	21.6 (3-36)	GOS	42 (42%)
Rosa et al. (2011)	102	30.5 ± 15.5	79/23	5.5 ± 1.6	6	GOS	36 (35%)
Shakir et al. (2016)	76	49.6 ± 19	53/23	NR	Discharge	Mortality	NR

Shibata et al. (1999)	30	NR	NR	NR	6	GOS	14 (47%)
Shibata et al. (2000)	17	35.5	11/6	7.3	Median = 4 (0.33-18)	GOS	6 (35%)
Shutter et al. (2004)	42	31 ± 16 (14-79)	28/14	5 ± 2 (3-8)	(6-12)	GOS	10 (24%)
Soldner et al. (2001)	30	26.9 (7-64)	23/7	NR	Discharge, 3, 12	GOS	12 (40%)
Tollard et al. (2009)	43	34.8 ± 12	40/3	6.6 ± 4·5	12	GOS	19 (44%)
Wang et al. (2008)	12	26 ± 8.1 (16-37)	8/4	4.4 ± 2.1 (3-8)	Discharge	GOSe	6 (50%)
Wang et al. (2014)	53	51.3 ± 11.4 (36-54)	35/18	NR	3	Mortality	NR
Warner et al. (2010)	25	26.8	18/7	6.2 ± 4.5	7.8 ± 1.9 (6-14)	GOSe	5 (20%)
Wedekind et al. (1999)	57	NR	NR	NR	(6-18)	GOS	30 (53%)
Wedekind et al. (2002)	40	NR	30/10	NR	11.3 (6-24)	GOS	17 (43%)
Weiss et al. (2008)	73	36 ± 14	58/15	6 ± 3	12	GOS	41 (56%)
Wilberger et al. (1987)	24	28 (15-53)	NR	NR	6	GOS	19 (21%)
Woischneck et al. (1999)	70	NR	NR	NR	6	Mortality	NR
Woischneck et al. (2008)	146	NR	NR	NR	Discharge, 36	GOS	21 (14%)

Woischneck et al. (2010)	100	37 (5-80)	72/28	NR	6	GOS	55 (55%)
Woischneck et al. (2010, 2011)	167	35 (1-86)	NR	NR	6	GOS	74 (44%)
Woischneck et al. (2015)	120	Median = 36 (2-86)	NR	NR	6	GOS	79 (66%)
Yanagawa et al. (2000)	34	27 ± 13.6	23/11	9.3 ± 3.3 (5-15)	3	GOS	7 (21%)
Yanagawa et al. (2009)	19	32.2 ± 3.9 (10-69)	17/2	5.8 ± 0.3 (3-8)	3	GOS	11 (58%)
Yu et al. (2012)	42	42.8 (8-80)	NR	NR	6	GOS	9 (21%)

Legend: GCS, Glasgow coma score; SD, standard deviation; GOS, Glasgow outcome scale; NR, not reported; GOSe, extended Glasgow outcome scale

2.15.2 Supplementary Table 2: MRI Characteristics of Included Studies

Study (year)	Time to MRI (days); Mean ± SD (Range)	MRI field strength (Tesla)	Sequences	Type of data reported
Bagley et al. (2000)	10.2 ± 7.4 (1-29)	1.5	T1, T2, T2*-GRE	Localisation
Bavetta et al. (1994)	20 (3-60)	0.08	NR	Size
Betz et al. (2012)	3.7 ± 6.1 (Within 28)	1.5	T1, T2, FLAIR, DTI	NR
Carpentier et al. (2006)	17.5 ± 6.4	1.5	T1, T2, T2*-GRE, FLAIR	Localisation, size
Chastain et al. (2009)	5.6 (0-24)	1.5	T1 SE, T2 dual SE, FLAIR	Size
Chelly et al. (2011)	7.7 ± 8.6 (1-60)	1.0	T1, T2, FLAIR	NR

Chew et al. (2012)	(0-35)	1.5	T1 SE, T2 SE, T2*-GRE, T2-Weighted FLAIR, DWI	Localisation, size
de la Plata et al. (2007)	(Within 14)	1.5	FLAIR	Size
Ding et al. (2008)	11 ± 10 (1-35)	3.0	T1, FLAIR	NR
Du et al. (2011)	9.5 (1-16)	3.0	T1, T2, FLAIR	NR
Firsching et al. (1998)	3.5 (Within 7)	1.5	T1, T2	Localisation
Firsching et al. (2001)	(Within 8)	1.5	T1, T2, TIRM	Localisation, score
Firsching et al. (2002)	(Within 7)	1.5	T1, T2	NR
Firsching et al. (2008)	Median = 3 (Within 7)	NR	NR	Score
Galanaud et al. (2012)	21 ± 9	1.5 – 3.0	T1, T2, T2*-GRE, FLAIR	NR
Garnett et al. (2000)	12 (3-35)	2.0	T1, T2	Type
Gerber et al. (2004)	26 (4-57)	1.5	T1 SE, T2 SE, T2*-GRE	NR
Godersky et al. (1990)	7 (2-19)	0.5 or 1.5	T1, T2	NR
Hilario et al. (2012)	Median = 17 (Within 30)	1.5	T1, T2, T2*-GRE, FLAIR	Localisation
Holshouser et al. (2006)	7 ± 4 (1-16)	1.5	T1, T2, SWI	Type
Hou et al. (2007)(	4.8 ± 2.6 (0-24)	1.5	T1, T2*GRE, FLAIR, DWI	NR
Iwamura et al. (2012)	11 ± 5.6 (Within 30)	1.5	T1, T2, FLAIR, SWI, DWI	Localisation, type
Janousek et al. (1999)	NR	NR	NR	NR
Kuchta et al. (2009)	3 (1-38)	1.5	T1, T2, T2*-GRE, FLAIR	Localisation
Lagares et al. (2009)	Median = 15 (Within 30)	NR	T2, T2*-GRE, FLAIR	Localisation, type, score
Ledig et al. (2015)	3.7 ± 4.2	NR	T1	Type
Lutkenhoff et al. (2013)	Median = 3	3.0	T1	Type
Lv et al. (2010)	(Within 30)	NR	NR	NR
Mannion et al. (2007)	Median = 1 (Within 3)	3.0	T2, T2*-GRE, FLAIR, Proton	Localisation, score
Marino et al. (2006)	(2-3)	1.5	T2, FLAIR	Localisation, type

Moen/Skandsen et al. (2010-2012, 2014)	Median = 8 (0-28)	1.5	T1-SE, T2-Turbo SE, T2*-GRE, FLAIR, DWI	Size, localisation, type, score
Paterakis et al. (2000)	(Within 2)	1.0	T1 Echo Planar, T2 Turbo SE, T2*-GRE, FLAIR	Localisation, type, score
Perez et al. (2014)	1.11 ± 0.66 (0-3)	3.0	NR	NR
Potapov et al. (2014)	(Within 21)	NR	T1, T2, T2*-GRE, FLAIR	Localisation, score
Prieto-Valderrey et al. (2013)	4.2 ± 4.7	1.5	T1, T2, FLAIR, DWI	NR
Reissberg et al. (2003)	5 (1-10)	1.5	T1, T2	NR
Rosa et al. (2011)	(1-3)	1.5	NR	NR
Shakir et al. (2016)	(1-13)	1.5	DWI	NR
Shibata et al. (1999)	10.3 (3-21)	NR	NR	Localisation
Shibata et al. (2000)	(Within 6)	0.5	T1, T2	Localisation
Shutter et al. (2004)	7 ± 4 (2-17)	1.5	T1, T2, T2*-GRE, SWI	Type
Soldner et al. (2001)	6 (2-34)	NR	T1, T2, T2*-GRE, FLAIR	NR
Tollard et al. (2009)	24 ± 11	1.5	T1, T2*-GRE, FLAIR	NR
Wang et al. (2008)	6.7 ± 4.2 (0-15)	3.0	T1, FLAIR, DTI	NR
Wang et al. (2014)	NR	NR	NR	Localisation
Warner et al. (2010)	2.5 ± 2.6 (0.5-9)	3.0	3D T1-Weighted Structural MPRAGE	NR
Wedekind et al. (1999)	14 (1-39)	1.0 or 1.5	T1, T2, T2*-GRE	Localisation
Wedekind et al. (2002)	12 (1-39)	1.0 or 1.5	T1 SE, T2 Fast SE, T2*-GRE	Localisation
Weiss et al. (2008)	26 ± 21	1.5	T1, T2*-GRE, FLAIR	Localisation
Wilberger et al. (1987)	(Within 5)	0.35-0.5	T1, T2	Localisation, type
Woischneck et al. (1999)	NR	1.5	T1, T2	Localisation
Woischneck et al. (2008)	(1-8)	1.5	T1, T2	Localisation
Woischneck et al. (2010)	4.2 (1-8)	1.5	T1, T2	NR
Woischneck et al. (2010, 2011)	(1-8)	1.5	T1, T2, T2*-GRE	Score
Woischneck et al. (2015)	3.8 (1-8)	1.5	T1, T2, FLAIR	Localisation

Yanagawa et al. (2000)	16.8 ± 5.6 (1-21)	1.5	T2-FSE, T2*-GRE	Size
Yanagawa et al. (2009)	16.8 ± 1.5 (5-27)	1.5	T2*-GRE	Size
Yu et al. (2012)	2 (Within 7)	NR	NR	Localisation

Legend: MRI, magnetic resonance imaging; SD, standard deviation; GRE, gradient echo; NR, not reported; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; SE, spin echo; DWI, diffusion weighted imaging; TIRM, turbo inversion recovery magnitude; MPRAGE, magnetization-prepared rapid gradient-echo

2.15.3 Supplementary Table 3: Relative Risk of Unfavourable GOS in Moderate and Severe TBI by Type of Focal Lesions on Acute MRI

Lesion Type	Studies	Subjects	RR	95% CI	I_2
Contusion	7	272	0.96	0.47 – 1.95	34%
Epidural Haematoma	3	73	1.00	0.47 – 2.11	0%
Subdural Haematoma	5	114	1.38	0.64 – 2.97	32%
Subarachnoid Haemorrhage	3	73	1.17	0.41 – 3.40	44%

2.15.4 Supplementary Table 4: Sensitivity Analyses for the Association of Brainstem Lesions with Unfavourable GOS in Moderate and Severe TBI

	Studies	Subjects	RR (95% CI)	I_2 (%)
Timing of outcome assessment:				
At 6 months	6	345	1.77 (1.12 to 2.80)	80
> 6 months	4	240	4.16 (2.30 to 7.54)	55
Mean timing of MRI post-TBI:				
≤ 7 days	2	70	1.39 (1.07 to 1.81)	0
> 7 days	7	387	3.89 (2.43 to 6.22)	59
MRI field strength:				
< 1.5 Tesla	3	121	2.28 (0.87 to 5.93)	87
≥ 1.5 Tesla	7	394	2.22 (1.38 to 3.56)	78
Confounding:				
Adequate control	2	203	8.67 (2.57 to 29.20)	60
Inadequate control	10	572	2.05 (1.50 to 2.82)	74
Methodological quality:				
Low or unclear risk of bias	3	241	5.84 (2.67 to 12.79)	62
High risk of bias	9	534	1.93 (1.39 to 2.69)	74

Legend: RR, relative risk; CI, confidence interval; MRI, magnetic resonance imaging; TBI, traumatic brain injury; GOS, Glasgow outcome score; DAI, diffuse axonal injury

2.15.5 Supplementary Table 5: Sensitivity Analysis for the Association of Shear Injury Compatible with Diffuse Axonal Injury with Unfavourable GOS in Moderate and Severe TBI

	Studies	Subjects	RR (95% CI)	I_2 (%)
MRI sequences:				
SWI and T2*GRE absent	3	51	1.46 (0.88 to 2.40)	14
SWI or T2*GRE employed	5	308	3.05 (1.33 to 7.03)	37

2.15.6 Supplementary Table 6: Summary of Evidence for Associations of Key Lesions with Mortality and Unfavourable Neurological Outcomes in Patients with TBI

Lesion	Outcome	No of participants (studies)	RR (95% CI)	Quality of Evidence (GRADE)
Brainstem	GOS	775 (12)	2.49 (1.72-3.58)	Moderate
Brainstem	Mortality	418 (5)	1.78 (1.01-3.15)	Low
Midbrain	GOS	692 (9)	1.87 (1.52-2.31)	Moderate
Pons	GOS	515 (6)	2.08 (1.79-2.43)	Moderate
Medulla	GOS	439 (4)	1.43 (0.93-2.18)	Low
Corpus Callosum	GOS	590 (8)	1.28 (0.71-2.30)	Low
Shear injury (DAI)	GOS	359 (8)	2.46 (1.06-5.69)	Moderate

Legend: RR, relative risk; CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; GOS, Glasgow outcome score; DAI, diffuse axonal injury

General Conclusion

Moderate and severe TBI are associated with high rates of mortality and long-term disability, are responsible for major direct and indirect healthcare costs, and can be a source of significant cascading social repercussions for family members or friends who support afflicted patients by taking on caregiver roles. The determination of prognosis early in the course of this condition is pivotal for informing acute clinical management and counseling substitute decision makers during discussions regarding level of intervention or resuscitation for the possibility of cardiopulmonary arrest. Recent research into clinical outcomes in moderate and severe TBI demonstrates that the decision by substitute decision makers to withdraw life sustaining therapy in the context of critical illness is a major pathway leading to death following TBI[59] and that these practices can be highly variable between centres.[59] As the decision to withdraw life sustaining therapies is frequently taken early, often within just days of the index trauma,[59] it is crucial that reliable acute-phase prognostic indicators are established to guide critical care physicians.

Considering its improving accessibility, employing MRI early in the care of these patients represents an advanced imaging modality which may serve as a novel prognostic indicator given the increasing feasibility of its application in the acute setting. As a highly sensitive neuroimaging modality, its potential ability to improve outcome prediction beyond CT coupled to its exclusion from other major observational studies of prognosis and prognostic model derivation studies in TBI have made it an attractive area of ongoing investigation as a complementary prognostic indicator early following neurotrauma.[65] The published literature studying the use of MRI in this setting spans nearly four decades, beginning roughly from the time of magnetic resonance technology's introduction into clinical practice up to modern day. This field therefore encompasses a vast evolution of MRI technology, the introduction of novel high sensitivity sequences, and the progressive improvement of post-acquisition image processing. Given this diversity in imaging protocols and the variability in how cerebral lesions have been studied, the ability for individual studies to directly inform clinical practice is limited and a need for cohesive evidence synthesis exists to permit effective and balanced knowledge translation into clinical practice.

The principle objective of this thesis was therefore to determine the prognostic value of cerebral lesion patterns visible on MRI performed in the acute phase of care for determining long-term clinical outcomes in patients having suffered moderate or severe TBI. To cohesively study the full spectrum of articles published on this topic, we undertook a high-sensitivity systematic review, without any exclusions based on lesion pattern studied or language of article publication, and performed pairwise random effects meta-analyses for all sufficiently homogeneous lesion-outcome analyses. Secondarily, this thesis sought to systematically assess the risk of bias of the studies published in this domain and determine the level of recommendation of the meta-analyses undertaken for each outcome in order to guide future research priorities in this field in addition to

informing clinicians on the confidence with which the final analyses can be made. This thesis contributes to the growing field of early risk assessment following TBI by providing objective data on the use of MRI in this population to assist long-term prognostication; it is the first systematic review and meta-analysis to quantitatively summarize the relationship between acute MRI lesion patterns and long-term clinical outcomes.

Our study established the prognostic value of several different patterns of brain lesions visible on early structural MRI as predictive of long-term clinical outcome. We demonstrated significant, strong relationships between the presence of lesions anywhere in the brainstem and both all-cause mortality (RR, 1.78; 95% CI, 1.01–3.15; I^2 = 43%) and unfavourable GOS (RR, 2.49; 95% CI 1.72–3.58; I^2 = 81%) at six months or greater follow-up. When the anatomical subdivisions of the brainstem were considered individually, this association remained statistically significant for lesions in both the midbrain and pons. Conversely, the presence of lesions in the corpus callosum, a structure superficial to the brainstem, were not found to significantly discriminate patient outcome. The presence of shear injury patterns suggestive of DAI was also heavily associated with unfavourable neurological outcome (RR, 2.46; 95% CI, 1.06–5.69; I^2 = 74%) and, importantly, subgroup analyses demonstrated that this relationship only remained significant in studies employing at least one of the two major susceptibility-sensitive sequences (either T2*-GRE or SWI), indicating the importance of such sequences in contemporary neurotrauma MRI protocols. Two scoring systems were used recurrently in multiple retrieved studies: the Firsching score[106] and the Adams-Gentry classification,[102] both of which classify patient MRIs in grades defined by the location of the deepest lesions visualized regardless of the presence or absence of higher lesions. In both classifications, the superficial-most grade is defined as being in the supratentorium (lobar white matter) and the deepest as being in the brainstem. Meta-analysis of studies presenting data for both scores demonstrated increasing risks of unfavourable neurological outcome as increasingly caudal structures were affected.

Globally, the findings of our meta-analyses are consistent with prior experimental preclinical models of TBI which have given rise to the current pathophysiological models thought to underpin the spectrum of injury and disability seen in TBI. In animal studies of TBI, where the severity of traumatic insults can be controlled and adjusted, the depth of traumatic lesions within the brain have been directly found to relate to the severity of the trauma.[170,171] Neurohistological studies performed during autopsy on patients with TBI have similarly demonstrated a relationship between lesion depth and mortality and duration of coma.[102] Maximal lesion depth is therefore a key determinant for the precise assessment of patient prognosis as this is likely a key mediator in the pathway between severity of trauma sustained and eventual clinical outcome. Based on this body of evidence, a “centripetal model” of TBI has been proposed, where the brain itself can be conceptualized as a funnel in which the force of trauma is transferred caudally, and the maximal depth achieved is a function of the trauma’s severity; in this proposed model, the grade of injury is determined by the caudal-most cerebral structure

receiving shear injury.[102] The findings of our meta-analysis support this model: the lesions most powerfully predictive of outcome were located in the brainstem and analysis of both of the depth-of-lesion scoring systems demonstrated progressively increasing risks of unfavourable neurological outcome with caudal grades. Brain MRI, specifically, is therefore a necessary modality for determining lesion depth accurately as CT cannot reliably assess the brainstem or other structures in the posterior fossa.

Although our systematic review was undertaken employing high-sensitivity search methods and methodology specifically adapted for prognostic factor studies when possible, several potential limitations exist which may constrain the direct clinical application of our findings. While we found consistent and statistically significant relationships between several lesion patterns and clinical outcomes in our primary analyses, the force of association varied considerably between studies for most analyses and we encountered high levels of heterogeneity as a result. While multifactorial in nature, the major portion of this heterogeneity is likely related to the broad nature of our inclusion criteria, resulting in potentially variable populations of TBI patients of differing acuity and trauma mechanisms to be included in our analyses. Additionally, a large amount of the heterogeneity may be attributable to the inherently observational design of studies examining prognosis in this field, leading to the possibility of significant and variable selection bias in the cohort of patients recruited and assessed. In particular, the majority of studies did not explicitly employ consecutive patient enrollment, a factor which may have led to lower acuity patients being overrepresented in such studies; this phenomenon may have attenuated the strength of some associations and possibly concealed the prognostic value of other MRI lesion patterns if the sickest patients were not recruited. Even in studies with consecutive patient enrollment, the impact of survival bias is likely not negligible as many of the highest acuity patients may have been too unstable to undergo MRI and subsequently died prior to being sent for neuroimaging. This survival bias is compounded by the fact that early mortality in the first few days following trauma is heavily driven by the decision to withdraw life-sustaining therapies, a practice shown to vary widely between centres, likely due variations in local practice patterns.[59] Except for the few prospectively conducted studies stipulating routine MRI in consecutively enrolled patients, the decision to undertake MRI in the majority of the included studies was at the discretion of the attending physician and thus susceptible to be selection bias and confounding by indication. Although in many of the included studies MRI was prospectively planned to be conducted for the express purpose of neuroprognostication, in some studies with retrospective designs this may not have been the case, contributing to the observed heterogeneity due to differences in scan protocols. Further, most studies did not adjust for potential confounders, presenting only univariable measures of association or crude outcome data. The potential for bias from confounding cannot therefore be excluded and the independence of any associations between lesion patterns on MRI and clinical outcomes cannot be determined from our data.

We explored possible sources of heterogeneity by undertaking subgroup analyses when possible according to trauma severity (GCS), the use of susceptibility sensitive MRI sequences, and anatomical subdivisions of the brainstem (among others) which partially aided in explaining this heterogeneity. Residual heterogeneity remained significant and may be due to numerous factors including variations between studies stemming from the evolution of MRI technology over time, the use or absence of semi-automated image processing, the exact sequences obtained, and MRI field strength. Beyond technological factors, studies differed on how they conceptualized injury: the term "lesion" has no standardized neuroradiological definition and no studies undertook post-mortem assessments to correlate specific MRI signal characteristics with underlying histopathological tissue injury. This is further compounded by the evolving nature of lesions not captured by MRI evaluation at a single point in time; the overall prognostic information detected may therefore be the result of multiple diverse pathophysiologic processes and cannot be directly attributable to a single primary or secondary process. Furthermore, the timing of outcome ascertainment was not uniform between studies and, in many instances, varied within study as well. Although mortality in TBI is frequently clustered in the early phase following trauma, patients' neurological deficits may evolve and improve over time, especially following prolonged rehabilitation; this is therefore poorly reflected in studies which solely evaluated patient outcomes at the time of hospital discharge. Primarily due to this non-consecutive patient selection and absence of control for confounding, almost all studies were rated at moderate or high risk of bias, a primary factor responsible for the overwhelmingly low to moderate confidence in our final analyses as assessed by the GRADE method. Lastly, although we designed a highly sensitive search strategy, we only applied our search to peer-reviewed journal publications and searches within grey literature were not performed, which may lead to the theoretical possibility of publication bias.

Several avenues of future research remain to be elucidated prior to the definitive implementation of MRI as a routine prognostic tool in the early assessment of patients with moderate or severe TBI. By employing a broad systematic search coupled with quantitative meta-analytic techniques, we have identified lesions patterns most consistently predictive of long-term all-cause mortality and neurological disability in patients with moderate or severe TBI; however, given the relatively low to modest level of confidence in our final results as determined by GRADE, these findings should be interpreted with caution until corroborated externally by high-quality independent data. Potential major areas requiring further investigation therefore include the need for confirmation of our study's findings in a large, contemporary cohort of TBI patients with the ability to control for large numbers of potential confounders. Furthermore, additional detailed MRI-centric studies should be undertaken to build upon our findings and perform head-to-head comparisons of specific sequences or scan protocols in moderate and severe TBI in order to determine which combinations of sequences maximizes clinical information while maintaining scan times brief in the acute setting. A major multicentre observational prognostic study in this field, the *TBI Prognosis* study,[172] has just been completed; MRI data was collected in a systematic

manner as part of this large prospective study, along with the collection of other clinical and paraclinical variables which should permit robust control of confounding and build upon the findings of this meta-analysis in order to determine whether the identified relationships remain statistically significant following multivariable analysis and thus maintain their prognostic value independent of other known independent prognostic indicators.

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