Comparative effectiveness of surgery for traumatic acute subdural hematoma

Essen, T.A. van

Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma

Thomas van Essen

Stellingen behorende bij het proefschrift

Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma

1. Neurosurgical evacuation of a traumatic acute subdural hematoma is a very effective intervention in a comatose patient.
   - This thesis -
2. Primum non nocere. When in equipoise on acute surgery or conservative treatment, treat patients with a traumatic acute subdural hematoma conservatively (initially).
   - This thesis, adapted from Hippocrates -
3. Primary decompressive craniectomy in traumatic acute subdural hematoma should be restricted to salvageable patients in whom immediate replacement of the bone flap is not possible.
   - This thesis -
4. For (acute) neurosurgical decisions, neurosurgeons have strong and consistent treatment preferences that are more influenced by center (training) culture and custom than by patient characteristics. The resulting treatment contrast between centers may be used in observational studies to challenge unmeasured confounding with instrumental variable analysis.
   - This thesis -
5. Instrumental variables are not a panacea.
   - Adapted from Rassen et al. 2009 -
6. While clinicians have become accustomed to interpreting and applying the results of randomized trials, this is not the case for observational studies (with instrumental variable analysis).
7. A strong collaboration between epidemiologists and clinicians is pivotal for clinical research, because each one separately lacks essential knowledge.
8. In case of clinical dilemmas, each patient should be included in a study because the alternative, perpetual uncertainty, is worse.
   - Adapted from Fredrickson DS. The field trial: some thoughts on the indispensable ordeal. Bull N Y Acad Med. 1968 Aug -
9. Using association terminology when implying causal effects is often a reflection of unsolved methodological flaws.
   - Adapted from Hernán MA. Am J Public Health 2018 -
10. People often underestimate the difficulty of doing clinical research well due to the ease of doing it poorly.
    - Adapted from jury verdict 2022 Rousseeuw Prize -
11. The success of an evidence-based neurosurgical practice lies in the ability to balance between - surgically inherent - intuitive rationalism and - epidemiology required - skeptical empiricism.
12. Succes is geen verdienste.
13. Een neurochirurg is niet de snelste maar is nooit te laat.
    - Adapted from Willem van Hanegem -

Colophon

The research described in this thesis was performed at the University Neurosurgical Center Holland, Departments of Neurosurgery, Leiden University Medical Center, Leiden, Haaglanden Medical Center and HAGA Teaching Hospital, The Hague, The Netherlands.

ISBN: 978-94-6361-846-5
Cover design: Thomas van Essen, Erwin Timmerman
Layout and printing: Optima Grafische Communicatie (www.ogc.nl)

Financial support by the 'Hersenstichting' (Dutch Brain Foundation), the European Union, Rembrandt Medical, B. Braun Medical, Integra Life, Daiichi Sankyo Nederland BV, ChipSoft and Krijnen Medical Innovations for the research and the publication of this thesis is gratefully acknowledged.

Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 8 juni 2023
klokke 10.00 uur

door

Thomas Arjan van Essen

PROMOTOREN
Prof. dr. W.C. Peul
Prof. dr. H.F. Lingsma (Erasmus MC - Universitair Medisch Centrum Rotterdam)

COPROMOTOR
Dr. G.C.W. de Ruiter

PROMOTIECOMMISSIE
Prof. dr. E.W. Steyerberg
Prof. dr. J. Horn (Amsterdam Universitair Medisch Centrum)
Prof. dr. W.P. Vandertop (Amsterdam Universitair Medisch Centrum)
Prof. dr. C. Dirven (Erasmus MC - Universitair Medisch Centrum Rotterdam)
Prof. dr. F. Rosendaal

CONTENTS

Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Traumatic brain injury

Traumatic brain injury (TBI) has a devastating impact on patients and their families. TBI, defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force,[1] is one of the greatest global healthcare problems. The yearly incidence varies widely per country with estimates ranging between 344 and 103 per 100,000 population (respectively in Asia and in the United States). TBI is the most important cause of death and disability in young adults and is one of the leading causes of injury-related death and disability across all other ages and in all countries. TBI represents 30–40% of all injury-related deaths, and neurological injury is projected to remain the most important cause of disability from neurological diseases until 2030 (2–3 times higher than the contribution from cerebrovascular disorders or Alzheimer's disease).[2-5]

TBI is typically categorized as primary or secondary brain injury. Primary brain injury describes the irreversible damage of the accident, before any emergency care has been given. Secondary brain injury describes the ensuing pathophysiological cascade which is not yet completely clarified but at least involves a complex interplay of neuroinflammation, hematological disturbances, metabolic disarray and neuronal cell death.[6]

Acute subdural hematoma

Sixty percent of patients with TBI needing hospitalization have intracranial hemorrhage. The most prevalent hemorrhages are focal hematomas, with acute subdural hematomas (ASDH) and intracerebral hematomas (ICH) being most prevalent (Figure 1). Another focal hematoma, the epidural hematoma (EDH) is rare. An ASDH after a traumatic head injury is the most lethal TBI despite treatment.[2,7,8]

Patients with an ASDH can experience a diverse array of symptoms, from deep coma or progressive neurological deterioration to slight headache with a focal deficit, and anything in between (Figure 2). This heterogeneity reflects a complex pathophysiology with many different injury types that may accompany ASDH.

Several terms have been used throughout history to describe ASDH such as pachymeningitis haemorrhagica, intradural hemorrhage, subdural hematoma, subacute subdural hematoma (as opposed to ASDH). While this terms all describe certain distinct characteristics, the expert consensus is to divide chronic and acute lesions. ASDH is herein defined as a subdural hematoma diagnosed within 14 days of TBI.[7]

The etiology distinguishes roughly between high-energy road traffic injuries, which are mostly motorized incidents, and low-energy incidental falls, which are typically

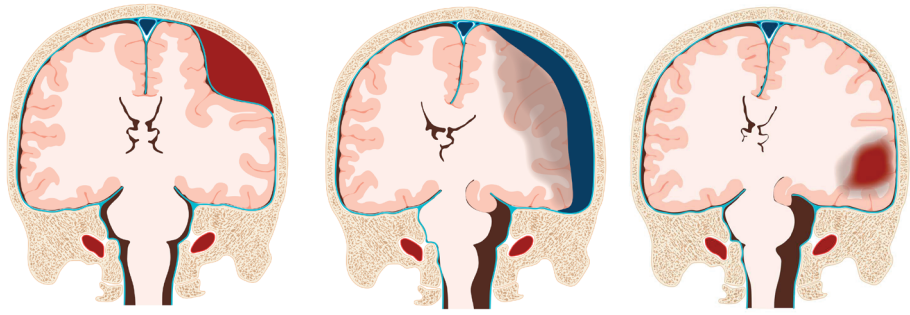


Figure 1. Different types of traumatic intracranial hematoma
(A) Epidural hematoma: a collection of blood between the skull and the outer membrane covering the brain (dura mater). Epidural hematomas are mostly arterial in origin and can thus expand rapidly, causing clinical deterioration and—if untreated—death. Treatment entails prompt surgical removal if symptomatic. (B) Subdural hematoma: a collection of blood located underneath the dura mater, generally associated with bruising of the underlying brain tissue (contusions). (C) Hemorrhagic contusion and intracerebral hematoma: lesions that reflect similar underlying pathologies, ranging from local bruising (contusions) to bleeding into the brain tissue (hematoma). Figure courtesy of Maartje Kunen, Medical Visuals, Arnhem, Netherlands. Reproduced with permission from Maas et al.[11]

ground level falls in the elderly.[9] Incidental falls mostly cause an isolated ASDH that originate from tearing of anchor venes intradurally. High velocity injuries induce several trauma mechanisms upon the brain. Acceleration and deceleration may cause shearing of neurons (diffuse axonal injury) and vessels.[10] Direct impact, whether a blow to the head or a head injury against an object, may result in bruising of the brain (contusion) and fracturing of the skull, sometimes leading to vascular rupturing. Hemorrhagic contusion injuries are frequently associated with ICH, which can progress in time and transform hemorrhagically, leading to a large intraparenchymal hematoma that sometimes also require surgical evacuation.
Thus, a TBI often constitutes of a combination of clinical diagnoses to describe the brain damage. The diverse clinical manifestation with the complicated etiopathophysiology has led to the denotation that TBI is 'the most complex disease in the most complex organ'.[12]

Immediate treatment decisions in acute subdural hematoma

Patients with an ASDH are usually treated non-surgically.[13] The non-surgical treatment strategy is best medical management that includes watchful monitoring on the hospital ward or management on the intensive care unit (ICU) with intracranial pressure (ICP) monitoring. Intensive care management aims to prevent brain ischemia by the initiation of ICP lowering treatments while also maintaining sufficient blood and oxygen supply to the brain. Surgical interventions can complement the ICU treatments to minimize the burden of raised ICP.

Surgical evacuation of an ASDH is commonly employed through a craniotomy or a decompressive craniectomy (DC). A craniotomy entails opening of the skin, removal of a piece of skull, removal of the hematoma clot, replacement of the skull flap and closure of the skin. In a DC the skull flap is left out prior to closing the skin.

The surgical intervention can be targeted causally, by evacuation of a focal hematoma, or symptomatically by opening the skull to reduce the (duration of) brain compression, typically to treat suspected or proven (refractory) raised ICP. By evacuation of the hematoma and, if indicated, performing concurrent DC, the raised ICP is assumed to normalize and outcome is thought to improve (Figure 2).

Whether to treat a patient surgically or conservatively is made on the basis of the neurological status of the patient, the size of the hematoma and the degree of the mass effect. Surgery has risks that have to be weighed against the risks of ensuing brain compression by the hematoma.[14] Primary DC is performed if the brain is bulging beyond the inner table of the skull intraoperatively, preventing the safe replacement of the bone flap without pathological ICP rise. Another reason is preventive; if there is concern that the brain may swell further in the first days after the operation. When the swelling goes down, the patient has another operation to reconstruct their skull, a cranioplasty. The associated risk of a cranioplasty are infection, cerebral edema and bone-flap reabsorption. The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, this type of operation may fail to control the brain swelling in some patients.

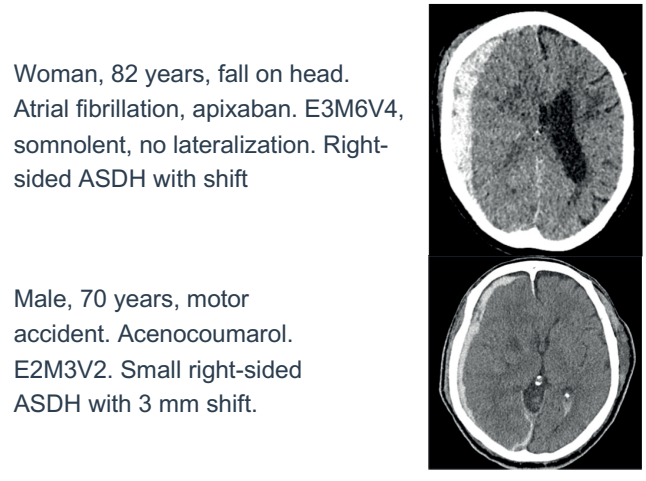


Figure 2. Hypothetical cases to illustrate the question clinicians are faced with in patients with an ASDH; to operate or not

Specifically, the question can broadly be divided into two typical patients: A) whether to evacuate the hematoma acutely or wait and monitor, possibly a delayed burr hole drainage, or B) in case of coma (Glasgow Coma Scale < 9) and a small ASDH, evacuate with (primary) DC or place an ICP sensor and evacuate in case of ICP rise.

The degree of brain compression is inferred from the decrease in consciousness level, expressed by the Glasgow Coma Scale (GCS), and the loss of pupil reactivity, an imminent sign of transtentorial herniation. In clinical practice, patients may present with multiple conditions, such as an ASDH combined with an ICH. The presence of concurrent pathologies affects the choice of treatment. Importantly, the surgical decision has to be made in far from ideal circumstances, in an emergency setting, often with incomplete clinical information and without the option to consult colleagues.

Current evidence

History

Several studies have played a pivotal role in shaping the course of treatment for ASDH throughout history. Although the evolution of the surgical evacuation of traumatic focal lesions starts very early in history (Figure 3), the path to the modern evaluation of the effect of surgery starts in the 20th century. In 1934 Munro shifted the viewpoint for the disease ASDH from 'being exclusively pathological' to 'more (frequently) surgical'.[15] Seelig and colleagues proved in 1981 the strong curative potential of surgery in ASDH by showing the sooner the better in comatose patients.[16] Several observations from fundamental studies of surgery in animals and hyperacute measurements of (human) ASDH perioperatively have, furthermore, elucidated mechanisms through which surgery may reduce damage of ASDH to the brain. Cerebral focal ischemia was shown to be the common denominator that explains the exceptional poor outcome of ASDH.[17] This ischemia can be caused by generalized pressure effects through raised ICP,[18] focal pressure effects from the hematoma,[19] metabolic derailments and local toxic effects,[20] especially in combination with ICH.[21,22] And although these studies show a multifactorial and sometimes contradictory genesis, the underlying translational theme is that the ischemia should be prevented.[23] Accordingly, the therapeutic mechanism of surgery extends beyond the effect of decompressing the brain by reducing the ICP, but it also serves to prevent local (neurotoxic) events that induce ischemia and worsen outcome.[24]

Current evidence

The Brain Trauma Foundation (BTF) has issued surgical guidelines (Figure 4). Surgery should be performed when the hematoma is significantly large irrespective of neurological condition ór in case of progressive neurological deterioration relatable to the lesion. These advices were based on observational studies with selected patients from single centres.[28-32] The guideline was issued in 2006, thus based on studies published before 2006 and there has been no update since then.[33]

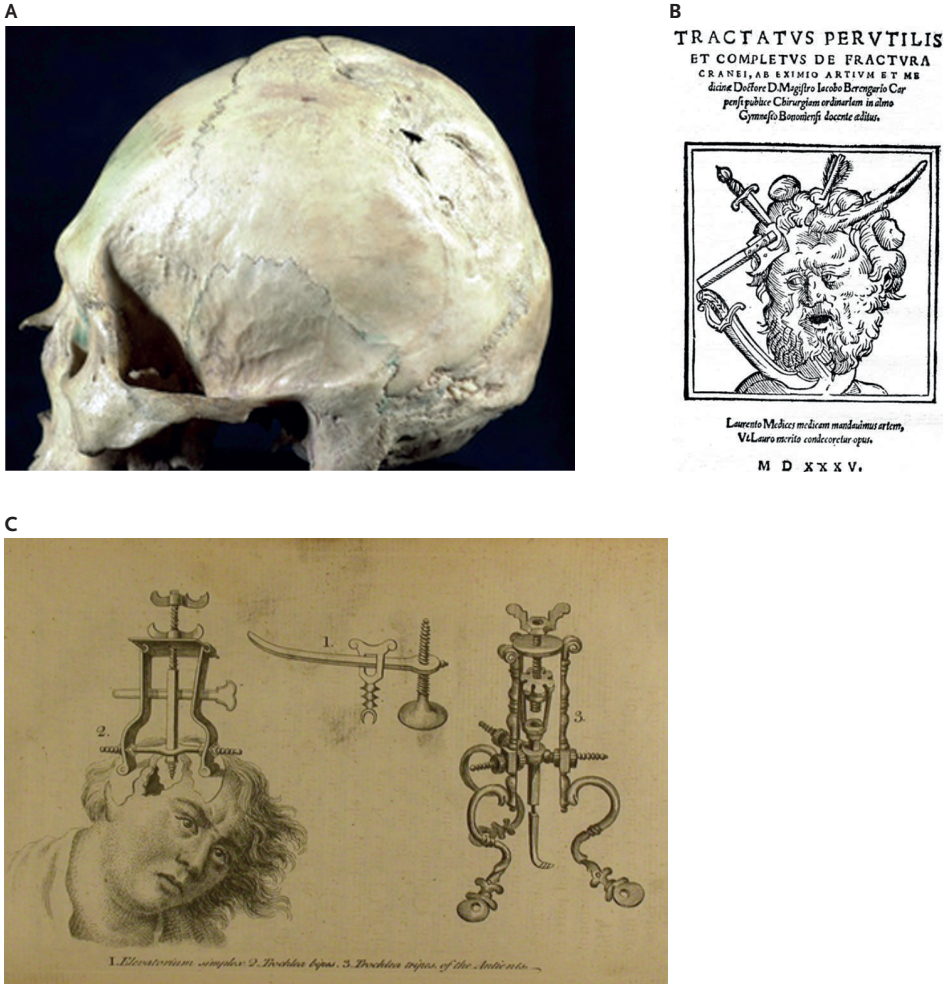


Figure 3. Brief history of the evolution of surgical evacuation in traumatic brain injury

Ancient man already knew that crushing the skull is the most effect method to eliminate an enemy. Concurrently, neurosurgical treatment with trepanation and burr-holes was devised to treat these injuries (mainly skull deformities). It might be the oldest surgical procedure with archaeological evidence dating back to the Neolithic period with anecdotal prove of trephinations for skull injuries already from 12,000 BC (A. The ancient skull has a large left parietal trephination with clear signs of antemortem healing. Adapted from [25]). In the Greco-Roman era, Hippocrates postulated - in line with his *do no harm* principle - that surgery below the dura is too dangerous to perform, restricting trephination for the treatment of skull injuries only, thereby setting the general consensus for surgery of the brain well up into the renaissance. The first systematic description of surgical indications for TBI, guidelines *avant la lettre*, have been written down by Jacopo (Giacomo) Berengario da Carpi (1470–1550) in 'Tractatus de Fractura Calvae sive Cranei' (B. Cover of the third edition of Berengario's Treatise on Skull Fractures, Venice, 1535).[26] He noted "..if the contused brain seems to be deeper than the surgeon's index finger, surgery is indicated" and in effort to introduce some cost-effectiveness considerations he mentions: "..surgery has a price and surgeons with experience in TBI are rare... therefore you must be prepared to pay for surgery... (the amount) equivalent to the price of a small house".

It was not until the 18th century, however, that the English surgeon Percivall Pott (1714–1788) shifted the predominant focus on skull to brain injuries and argued that surgery of the skull should go alongside an appreciation of whether or not it should be accompanied by treatment of accumulated blood under the skull (C. A illustration from Pott's work on head injuries detailing the "tripod" style of trephine that he favored. From Pott P: The Chirurgical Works of Percival Pott. London: Hawke, W. Clarke, R. Collins, 1775). He suggested that the symptoms seen in head injury might be due to direct injury of the brain and not due to just skull injury, and that the distinction should be made between compression and concussion of the brain when evaluating a head injury.[25]

While these historical anecdotes certainly have some medical and surgical merits, surgery in general probably did more harm than good until the 20th century.[27] It was not until the introduction of anesthesia and antisepsis in 1867, by Sir Joseph Lister (1827–1912), that surgeries of the skull were becoming safer.

The BTF acknowledged the lack of high-quality evidence and advised to conduct well-conducted comparative studies on surgery vs conservative treatment in ASDH. Thus, observational studies have provided valuable insights but the effectiveness of surgery remains unclear.

Surgical Management of Acute Subdural Hematomas

RECOMMENDATIONS
(see *Methodology*)

Indications for Surgery

- An acute subdural hematoma (SDH) with a thickness greater than 10 mm *or* a midline shift greater than 5 mm on computed tomographic (CT) scan should be surgically evacuated, regardless of the patient's Glasgow Coma Scale (GCS) score.
- All patients with acute SDH in coma (GCS score less than 9) should undergo intracranial pressure (ICP) monitoring.
- A comatose patient (GCS score less than 9) with an SDH less than 10-mm thick and a midline shift less than 5 mm should undergo surgical evacuation of the lesion if the GCS score decreased between the time of injury and hospital admission by 2 or more points on the GCS and/or the patient presents with asymmetric or fixed and dilated pupils and/or the ICP exceeds 20 mm Hg.

Timing

- In patients with acute SDH and indications for surgery, surgical evacuation should be performed as soon as possible.

Methods

- If surgical evacuation of an acute SDH in a comatose patient (GCS $<$ 9) is indicated, it should be performed using a craniotomy with or without bone flap removal and duraplasty.

KEY WORDS: Coma, Computed tomographic parameters, Craniotomy, Decompressive craniectomy, Head injury, Hematoma, Intracranial pressure monitoring, Salvageability, Subdural, Surgical technique, Timing of surgery, Traumatic brain injury

Figure 4. Brain Trauma Foundation guidelines regarding surgical indications in acute subdural hematoma.[34,35]

Generating new evidence

With well-known limits in time, money and other resources, clinical research should be focused on answering questions that directly result from daily clinical practice, are thus clinically relevant.[36] Although surgical evacuation of an ASDH is the most frequently performed acute surgical intervention within the skull,[37] its effectiveness relies on the lowest category on the evidence hierarchy.[38] Many neurosurgical intervention, especially acute surgery in TBI, have become well established before the methodological principles of evidence-based medicine became common practice. Although this may explain part of the lack of high-quality evidence, there is not a single explanation why a higher evidence level has not been attained since then. A part maybe explained by the fact that TBI surgery is considered common sense. The analogy to the effectiveness of a parachute is made (Figure 5), even by authorities in the field.[37]

Figure 5. In 2002 Smith and Pell published "Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials."
In poking fun at those who demand randomized controlled trial evidence to support therapeutic intervention, they use the parachute as an example of an imperfect intervention for which no randomized controlled trial evidence exists, sensibly enough suggest that no one is likely to volunteer to participate in such a trial. This common sense is applied to many interventions among which one is acute surgery for acute subdural hematoma. This extrapolation attests to the intractable opinion held among neurosurgeons of ASDH being a purely a surgical disease and underestimates the complexity of the disease.

This analogy disregards the complexity of the disease: it is not merely a matter of assuming a lower ICP will lead to a good outcome. Every (new) intervention in health care should be accompanied by a proper assessment of its benefit and harms. RCTs provide the strongest evidence on the effectiveness of medical interventions.[39-41] However, there is an abundance of literature showing the lack of successful RCTs in neurosurgery.[42-45] RCTs in neurosurgery are difficult to conduct due to methodological, pragmatic and sometimes ethical constraints. Investigating surgical interventions involves particular challenges compared to non-surgical medical research because of the complexity of (peri)operative procedures, surgical learning curves, patients' and surgeons' equipoise, blinding issues, and cultural or psychological barriers towards the use of randomization. For the specific challenges posed by surgical research, the IDEAL (Idea, Development, Exploration, Assessment, Long-term) framework guides researchers and clinicians in evaluating surgical interventions.[46] Specific for TBI are the heterogeneity of the population and interventions, the emergency setting of an acutely life-threatening condition, limited patient information in the absence of proxies and the largely unknown pathophysiological mechanisms of brain injury.[47,48] This failure of RCTs goes along a significant waste of clinical data and resources, and stands in stark contrast to the need for updated surgical guidelines and burden incurred by TBI.

The extent to which classical observational studies can inform treatment decision is limited. Observational studies of intervention are prone for bias, i.e. potential differences in outcome between intervention groups could also be explained by other factors than the intervention under study. When using observational studies, careful decisions in data collection and analysis should be made to allow causal interpretation.[49]

Therefore, the second-best study design is a prospective high-quality observational comparative effectiveness study, also referred to as a form of comparative effectiveness research (CER).[50] CER studies have gained popularity over the years.[48] Although principally inferior to RCTs with regard to internal validity, more advanced analysis such as instrumental variable analysis can lead to causal inference closely resembling RCTs (Figure 6).[51] There have been many precedents of these observational studies that directly impacted clinical practice.[52-55] The appealing aspect in TBI to use CER is the fact that there might be large practice variations due to the absence of high-quality evidence, possibly a result of the strong treatment preferences of the neurosurgical mindset. These possible large variations in care and outcome are worthwhile to investigate because recognizing beneficial treatment strategies may far outweigh any benefit that realistically can be expected from a new intervention.[56]

Thus, there is a clear role for conducting high-quality observational studies with sophisticated analyses to inform practice.

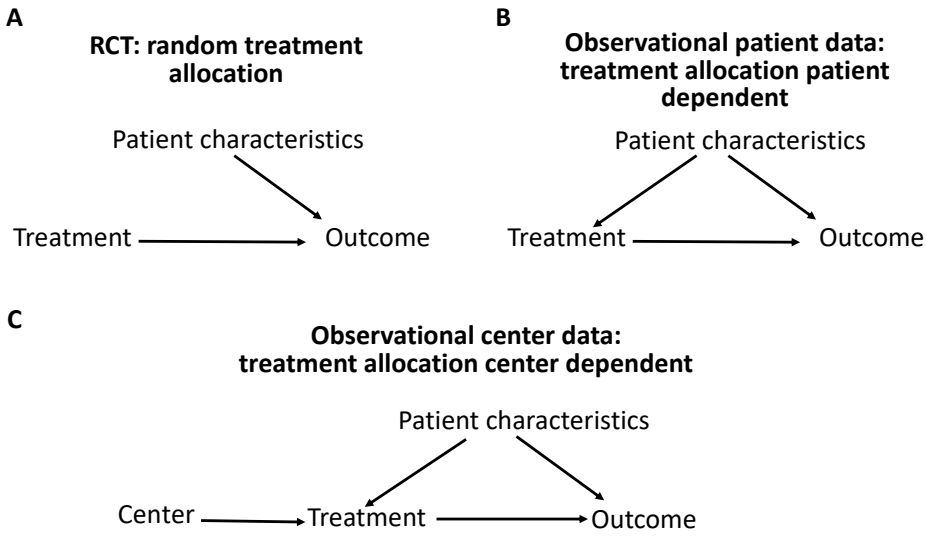


Figure 6. Instrumental variable (IV) analysis to reduce confounding by indication, as compared to randomization in randomized controlled trials (RCTs) and to traditional analysis in observational studies

Randomization separates treatment from patient characteristics and thereby ensures no confounding when estimating the effect of treatment on outcome (A). Effect estimation in observational data relies on statistical correction (f.e. regression modelling or propensity scores) but unmeasured confounding may remain a problem (B). In IV analysis (C), the instrumental variable center 'allocates' patients to be exposed to different likelihoods of receiving treatment. In analyzing treatment as center characteristic instead of a patient characteristic the intervention is again independent from the patient characteristics (no arrow from patient characteristics to center, just like with randomization).

Datasets used in this thesis

CENTER-TBI

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study was an international observational cohort study in centers across Europe and Israel, including patients between December 19th 2014 and December 17th 2017.

The aims of CENTER-TBI were to provide new, multidimensional insight into TBI characterization and to determine effectiveness of several treatment interventions in TBI.[12,57]

In total 4559 patients from 65 centers were included in the core study, which collected data on demographics, injury, imaging, monitoring, treatment, and outcomes up to 1-year post-injury (Figure 7). Provider profiling questionnaires captured the structures and processes of care of participating centers.

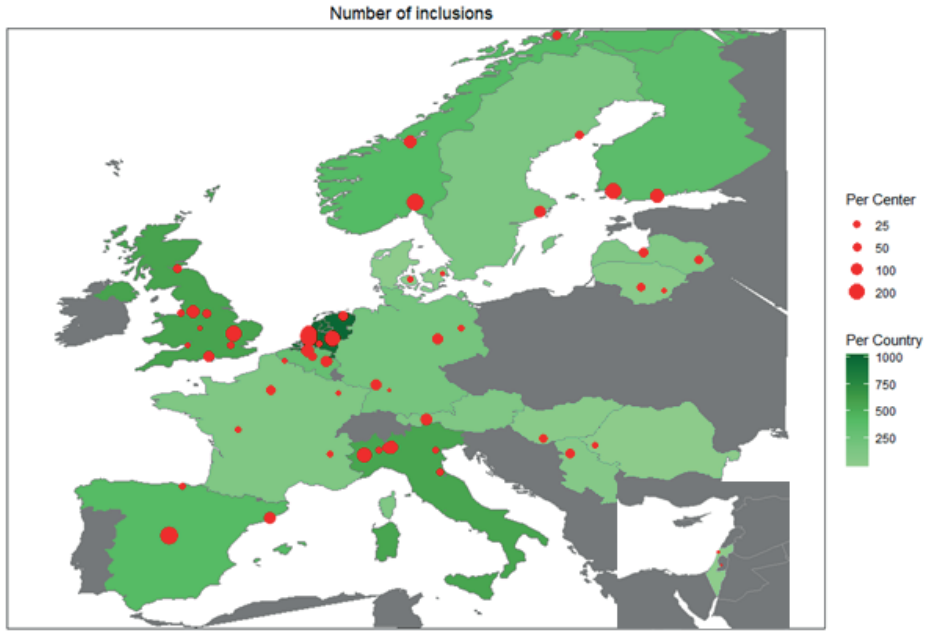


Figure 7. Participation per study center and country in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Core study (n=4509 patients).

Net-QuRe

The Neurotrauma Quality Registry (Net-QuRe) is a multi-center, prospective, observational cohort study designed to form the basis of a quality registry for moderate and severe TBI in The Netherlands.[58,59]

Five level 1 trauma centers and eight rehabilitation facilities in The Netherlands partook in Net-QuRe. All trauma centers serve a regional function for neurosurgical care in geographically distinct areas. One of the trauma centers consists of three separate hospitals, all of which facilitate complex neurocritical care.

Inclusion started in January 1, 2015 along with the commencement of the overarching CENTER-TBI project and continued after its completion until the 1st of January, 2020. 937 patients were included. Next to general demographic measures, process measures were collected. Data were gathered during admission in the hospital and also in the rehabilitation center. Outcome measures are collected at 6, 12 and 24 months after hospital discharge.

In the studies in this thesis, we used the core study and provider profiling of CENTER-TBI, as well as the Net-QuRe dataset.

Objectives

The overall aim of this thesis is to evaluate the comparative effectiveness of treatment approaches for patients with ASDH. This aim led to the following research questions:

I. What is the current evidence on the effectiveness of surgical treatment of ASDH?
II. What is the current practice in treatment of patients with ASDH in Europe?
III. Which study designs and analyses are suited to determine the effectiveness of surgical treatment of ASDH?
IV. What is the effectiveness of different treatment approaches (surgery versus initial conservative treatment and decompressive craniectomy versus craniotomy) for ASDH?

OUTLINE OF THE THESIS

In **Part I** the current evidence base for neurosurgical interventions in TBI is addressed. Chapter 2 provides an overview of recent effectiveness studies on neurosurgical interventions and describes the neurosurgical considerations in the treatment of patients with TBI. Chapter 3 is a systematic review of the available comparative studies on surgery in ASDH

In **Part II** I present the current state of neurosurgical management of TBI in Europe (Chapter 4) with an emphasis on the treatment of ASDH (Chapter 5).

Part III focuses on how to properly design a study aiming to measure the effectiveness of neurosurgical interventions (Chapter 6) with a focus on how to deal with confounding in observational studies on acute neurosurgical decompression in focal lesions (Chapter 7). Chapter 8 presents the study protocol, which discusses the choices made in the design and conduct of the prospective observational studies CENTER-TBI and Net-QuRe to determine the comparative effectiveness of acute surgery vs conservative treatment for ASDH and ICH. The protocol has been published for transparency and accountability, and to inspire subsequent observational effectiveness studies on surgical interventions. The presented study with regard to early surgical intervention in ICH is not part of this thesis.

The studies in **Part IV** aim to compare the effectiveness of surgical treatment approaches in ASDH. First, a retrospective observational study with routinely available data is presented in Chapter 9. The study is conducted in the centers of our survey (Chapter 4) that had the most divergent views on the acute management of ASDH. Chapter 10 describes the results of the observational study with regard to the effectiveness of a strategy of acute neurosurgical decompression in ASDH, in terms of both objective and subjective outcomes. Chapter 11 is a reply to a letter to the editor. This letter is a reaction on the effectiveness study in Chapter 10 and

serves as an example of the response among the neurosurgical community. Chapter 12 presents the study with regard to DC as compared to craniotomy in ASDH.
In **Part V** we summarize the preceding chapters and discuss the relevance, limitations and clinical implications of our findings. We end by providing suggestions for future research.

REFERENCES

1. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010;91(11):1637–40.
2. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology* 2008;7(8):728–41.
3. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol.* 2013 Apr;9(4):231-6.
4. World Health Organisation (WHO). Neurological disorders: public health challenges. 2006. http://www.who.int/mental_health/neurology/neurological_disorders_report_web.pdf (accessed March 1, 2022).
5. Rubiano AM, Carney N, Chesnut R, Puyana JC. Global neurotrauma research challenges and opportunities. *Nature* 2015;527(7578):S193–7.
6. Rosenfeld JV, Maas AI, Bragge P, et al. Early management of severe traumatic brain injury. *Lancet* 2012;380(9847):1088–98.
7. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006;58(3 Suppl):S16–24–discussionSi–iv.
8. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017;16(12):987–1048.
9. Steyerberg EW, EW, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *The Lancet Neurology* 2019;18(10):923–34.
10. Gennarelli TA, Thibault LE. Biomechanics of acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1982;22(8):680–6.
11. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12):987–1048.
12. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76(1):67–80.
13. Bajsarowicz P, Prakash I, Lamoureux J, et al. Nonsurgical acute traumatic subdural hematoma: what is the risk? *Journal of Neurosurgery* 2015;123(5):1176–83.
14. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurgical FOCUS* 2009;:1–16.
15. Munro D. The diagnosis and treatment of subdural hematoma. *N Engl J Med* 1934;210(22):1–16.
16. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981;304(25):1511–8.
17. Macpherson P, Graham DI. Correlation between angiographic findings and the ischaemia of head injury. *Journal of Neurology, Neurosurgery & Psychiatry* 1978;41(2):122–7.
18. Verweij BH, Muizelaar JP, Vinas FC. Hyperacute measurement of intracranial pressure, cerebral perfusion pressure, jugular venous oxygen saturation, and laser Doppler flowmetry, before and during removal of traumatic acute subdural hematoma. *Journal of Neurosurgery* 2001;95(4):569–72.
19. Valadka AB, Gopinath SP, Robertson CS. Midline shift after severe head injury: pathophysiologic implications. *The Journal of Trauma: Injury, Infection, and Critical Care* 2000;49(1):1–8–discussion8–10.
20. Miller JD, Bullock R, Graham DI, Chen MH, Teasdale GM. Ischemic brain damage in a model of acute subdural hematoma. Neurosurgery 1990;27(3):433–9.
21. Patel TR, Schielke GP, Hoff JT, Keep RF, Lorris Betz A. Comparison of cerebral blood flow and injury following intracerebral and subdural hematoma in the rat. *Brain Res* 1999;829(1-2):125–33.
22. Kawamata T, Katayama Y. Cerebral contusion: a role model for lesion progression. *Progress in Brain Research* 2007;161:235–41.
23. Sawauchi S, Marmarou A, Beaumont A, et al. Acute subdural hematoma associated with diffuse brain injury and hypoxemia in the rat: effect of surgical evacuation of the hematoma. *Journal of Neurotrauma* 2004;21(5):563–73.
24. Servadei F, Compagnone C, Sahuquillo J. The role of surgery in traumatic brain injury. *Curr Opin Crit Care* 2007;13(2):163–8.
25. Goodrich JT. How to get in and out of the skull: from tumi to "hammer and chisel" to the Gigli saw and the osteoplastic flap. *Neurosurgical FOCUS* 2014;36(4):E6.
26. Di Ieva A, Gaetani P, Matula C, et al. Berengario da Carpi: a pioneer in

neurotraumatology. *Journal of Neurosurgery* 2011;114(5):1461–70.
27. Wootton D. Bad Medicine: Doctors Doing Harm Since Hippocrates. *Oxford University Press, USA*; 2007.
28. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993;121(3-4):100–8.
29. Wong. Criteria for conservative treatment of supratentorial acute subdural haematomas. *Acta Neurochir Wien* 2005;(135):38–43.
30. Servadei F, Nasi MT, Cremonini AM, Giuliani G, Cenni P, Nanni A. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998;44(5):868–73.
31. Choksey M, Crockard HA, Sandilands M. Acute traumatic intracerebral haematomas: determinants of outcome in a retrospective series of 202 cases. *Br J Neurosurg* 1993;7(6):611–22.
32. Katayama Y, Tsubokawa T, Miyazaki S, Kawamata T, Yoshino A. Oedema fluid formation within contused brain tissue as a cause of medically uncontrollable elevation of intracranial pressure: the role of surgical therapy. *Acta Neurochir Suppl (Wien)* 1990;51:308–10.
33. Vega RA, Valadka AB. Natural History of Acute Subdural Hematoma. *Neurosurgery clinics of North America* 2017;28(2):247–55.
34. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. Neurosurgery 2006;58(3 Suppl):S16–24–discussionSi–iv.
35. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006;58(3 Suppl):S25–46–discussionSi–iv.
36. Stam J, Renckens C, Bouma J, Hijdra A, Van Gijn J, Vermeulen R. De Kritieken. Amsterdam: *Off Page*; 2011.
37. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005;1183–92.
38. Howick J, Library ICJL, Glasziou P, et al. "The Oxford Levels of Evidence 2." *Oxford Centre for Evidence-Based Medicine*. Available from: http://www.cebm.net/index.aspx?o=5653
39. Nelson KS, Brearley AM, Haines SJ. Evidence-based assessment of well-established interventions: the parachute and the epidural hematoma. *Neurosurgery* 2014;75(5):552–9–discussion559.
40. Sackett DL, Haynes RB, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. *Lippincott Williams and Wilkins*; 1985.
41. Rothman KJ. Epidemiology: An Introduction. *Oxford University Press;* 2012.
42. Schöller K, Tonn J-C. Guiding neurosurgery by evidence, Editor: B.E. Pollock. *Acta Neurochir* 2010;152(1):183–3.
43. Mansouri A, Cooper B, Shin SM, Kondziolka D. Randomized controlled trials and neurosurgery: the ideal fit or should alternative methodologies be considered? *Journal of Neurosurgery* 2016;124(2):558–68.
44. Martin E, Muskens IS, Senders JT, et al. Randomized controlled trials comparing surgery to non-operative management in neurosurgery: a systematic review. *Acta Neurochir (Wien)*. 2019;1–8.
45. Volovici V, Steyerberg EW, Cnossen MC, et al. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. *Journal of Neurotrauma* 2019;36(22):3183–9.
46. McCulloch P, Altman DG, Flum DR, et al. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009;374(9695):1105–12.
47. Maas AIR, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-Orientation of Clinical Research in Traumatic Brain Injury: Report of an International Workshop on Comparative Effectiveness Research. *Journal of Neurotrauma* 2012;29(1):32–46.
48. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurgical FOCUS* 2012;33(1):E3.
49. Hernán M, Robins J. Causal Inference: What If. *Boca Raton: Chapman & Hall/CRC*; 2020.
50. Initial National Priorities for Comparative Effectiveness Research. Washington, D.C.: *National Academies Press*; 2009.
51. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *American Journal of Epidemiology* 2016;183(8):758–64.
52. Jakola AS, Myrmel KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. *JAMA* 2012;308(18):1881–8.

53. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363–9.
54. Laborde-Castérot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. *Journal of Clinical Epidemiology* 2015;68(10):1232–40.
55. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007;297(3):278–85.
56. Lingsma HF, Roozenbeek B, Li B, et al. Large Between-Center Differences in Outcome After Moderate and Severe Traumatic Brain Injury in the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) Study. *Neurosurgery* 2011;68(3):601–8.
57. Maas AIR. CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI. *Clinicaltrials.gov* 2014.
58. Nederlands Trial Register. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.
59. The 3rd Joint Symposium of the International and National Neurotrauma Societies and AANS/CNS Section on Neurotrauma and Critical Care August 11–16, 2018 Toronto, Canada. *Journal of Neurotrauma* 2018;35(16):A–1–A–285.

PART I

CURRENT EVIDENCE

Chapter 2

Surgical management of traumatic brain injury – to operate or not

Adapted from:
Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research.
Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Büki A, Chesnut RM, Citerio G, Coburn M, Cooper DJ, Crowder AT, Czeiter E, Czosnyka M, Diaz-Arrastia R, Dreier JP, Duhaime AC, Ercole A, Van Essen TA, Feigin VL, Gao G, Giacino J, Gonzalez-Lara LE, Gruen RL, Gupta D, Hartings JA, Hill S, Jiang JY, Ketharanathan N, Kompanje EJO, Lanyon L, Laureys S, Lecky F, Levin H, Lingsma HF, Maegele M, Majdan M, Manley G, Marsteller J, Mascia L, McFadyen C, Mondello S, Newcombe V, Palotie A, Parizel PM, Peul W, Piercy J, Polinder S, Puybasset L, Rasmussen TE, Rossaint R, Smielewski P, Söderberg J, Stanworth SJ, Stein MB, von Steinbüchel N, Stewart W, Steyerberg EW, Stocchetti N, Synnot A, Te Ao B, Tenovuo O, Theadom A, Tibboel D, Videtta W, Wang KKW, Williams WH, Wilson L, Yaffe K; InTBIR Participants and Investigators.

The Lancet Neurol. 2017 Dec;16(12):987-1048.

And

Surgical dilemmas in traumatic brain injury
Van Essen TA, De Ruiter GCW, Den Boogert HF, Volovici V, Maas AIR, Peul WC.

Tijdschr Neurol Neurochir 2018;119(2):46-51)

SUMMARY

Traumatic brain injury has a high mortality and those patients that survive often experience long-term disability due to physical, cognitive or psychological deficits. Neurosurgical interventions in traumatic brain injury can cause major reductions in mortality and morbidity. However, the precise indications of surgery in traumatic brain injury are not sufficiently clear. As a consequence, treatment varies among regions, hospitals and neurosurgeons. Recent, current and future research is rapidly changing this uncertainty. Pragmatic studies with a so-called comparative effectiveness design seem to be the most promising to increase the level of evidence of neurosurgical interventions in traumatic brain injury.

INTRODUCTION

One of the most vexing problems in the neurosurgical care for brain trauma patients is to determine which patients might benefit from surgical treatment for traumatic intracranial hematoma's and/or raised intracranial pressure. This is complicated by additional uncertainty regarding the optimal timing of surgery and the most effective technique, in particular in cases with large contusions and in patients considered for decompressive craniectomy (DC). The goals of the initial surgical treatment in TBI are to remove space-occupying intracranial hematomas, and to decrease pressure on the brain in order to prevent or minimize damage to important brain structures and to prevent life-threatening herniation events. Surgical decompression can be achieved by evacuation of a hematoma, by insertion of an external ventricular drain for drainage of cerebrospinal fluid (CSF), or by removing a large part of the skull to alleviate raised intracranial pressure resulting from swelling of the brain.[1-3] The latter procedure, called decompressive craniectomy (DC), may be performed in the same setting as the evacuation of a hematoma or later to treat diffuse brain swelling that is refractory to conservative medical management. Evacuation of an intracranial hematoma may be considered a causal approach, whilst DC is more symptomatic.

The majority of emergency TBI neurosurgery is directed at evacuating hematomas.[4] The hematoma may be located inside the brain (contusion) or outside the brain, above (epidural hematoma (EDH)) or below (acute subdural hematoma (ASDH, figure 1)) the outermost covering of the brain (dura mater).

ASDH and contusions, which are sometimes called intracerebral hematomas, represent the major clinical dilemmas. The occurrence of an ASDH is estimated to be up to 11% in patients with TBI and up to 49% of the patients with severe TBI (GCS < 9).[5,6] Large cerebral contusions are observed in 8% of all TBI, in up to 35% of severe TBI,[7] sometimes together with an ASDH, and in one study contusions were seen in 73% of patients with moderate and severe TBI as diagnosed on MRI.[8]

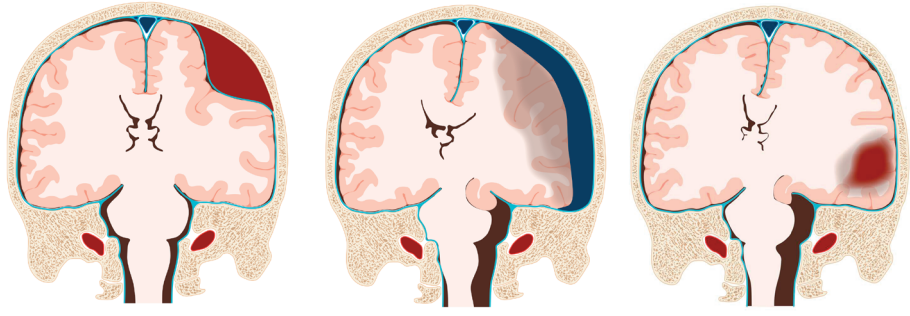


Figure 1. Different types of post-traumatic intracranial hematomas: A: epidural; B: subdural hematoma; C: intracerebral hematoma or contusion

Whereas international consensus exists with regard to the necessity for evacuation of a moderately sized or large EDH, heterogeneity exists in decision-making for ASDH, for contusions and for refractory raised intracranial pressure. This leads to considerable practice variation. The focus of this review is on the clinical specificities of the surgical indications and on the evidence underpinning these decisions.

FACTORS INFLUENCING SURGICAL DECISION-MAKING IN TBI

Many clinical factors may influence the choice and timing of surgical treatment, including patient related factors, surgeon preference, patient and family wishes, religion and cultural background, as well as logistic considerations. Patient factors include the initial GCS, pupillary size and reactivity, extracranial injuries, the severity of the injury, structural abnormalities on the CT scan and comorbidity as determinants of the balance between benefit and risk or futility. One of the most important factors, however, seems to be the preference and (lack of) experience of the treating neurosurgeon! When confronted with a patient with traumatic ASDH and/or contusion the neurosurgeon on-call is faced with several challenging management decisions.[2] Before choosing what type of surgery to perform, the first decision is whether or not surgery should be performed. Surgery might save a patient's life and preserve neurological function.[9] However, some patients may survive by surgery, but others may have an unfavorable functional outcome,[10-12] ranging from severe neurological and cognitive deficits to a persistent vegetative state. Conversely, surgery may not always be necessary and a substantial portion of patients managed conservatively have favorable outcomes.[13-15] Furthermore, certain subgroups may not benefit from surgery because the primary damage is simply too devastating. Too liberal surgical indications may lead to an increased number of survivors with severe disabilities, but inappropriate conservative management may result in unnecessary deaths. The decision to operate or not is not only based on medical considerations of expected mortality and functional outcome, but also on ethical considerations. The patient and relatives view towards a meaningful quality of life might be different from our medical perception of favorable outcome. Notably, the view on a worthwhile outcome can greatly differ between the clinician and the patient/relatives, not seldom due to cultural and religious standpoints. Sometimes, when there is enough time and opportunity to discuss the expected outcome with the relatives, this personal view on quality of life can be taken into account. Thus, the decision whether to operate or not does not merely depend on rational factors, but also involves several intuitive and ethical issues.

Furthermore, an important aspect of surgical approach is the timing of surgery. This relates specifically to intracerebral hematomas/contusions since it is generally agreed

upon that early surgery is better than delayed for ASDH and EDH. Sometimes, a contusion is initially managed conservatively, but may later be treated surgically by bony decompression or removal of contused brain tissue because of secondary deterioration. Indeed, a study conducted by the European Brain Injury Consortium reported that 73% of patients undergoing a delayed DC had developed raised ICP due to a contusion or intra-cerebral hemorrhage.[4]

These complex decisions often have to be made in difficult circumstances, constrained by time.[9] and in absence of peer consultation. As a result, the decision is often based on intuition and experience of the surgeon, which is not a rational evidence-based approach.

EVIDENCE UNDERPINNING SURGICAL DECISION-MAKING IN TBI

Surgical guidelines have been developed but lack robust scientific grounds.[1] The guidelines recommend that every ASDH with a thickness more than 10 mm and midline shift over 5 mm should be evacuated as soon as possible, irrespective of the neurological condition. For contusions the guidelines advocate to evacuate all lesions above 50 cm^3, and above 20 cm^3 in case of a GCS 6-8 with midline shift of at least 5 mm and/or cisternal compression on CT. These guidelines were based on low grade evidence (level III) derived from retrospective studies of small groups of selected patients, published more than 10 years ago. While additional studies have emerged,[6,10] these studies have only marginally improved the evidence base in this context.

Consequently, many different opinions exist between neurosurgeons as to what constitutes best surgical practice. Controversy is probably greatest with regard to the management of intracerebral contusions: in some countries contusions are routinely operated upon early to prevent deterioration (pre-emptive approach), whilst in others a conservative approach is preferred and patients only seldom operated.[4,16] The variation in surgery for ASDH lies not so much in the timing, since benefits of early surgery have been established, but more in the stance towards which subgroups of patients can benefit from evacuation.[5] Moreover, there is a large difference in point of view among neurosurgeons with respect to combining the evacuation of an ASDH with a DC.[17]

This paucity of high quality evidence on surgical management for TBI is partly explained by the difficulty of performing RCTs in TBI in general.[18] The heterogeneous study population, presence of other injuries, different mechanisms of injury, and the multitude of treatment variables, together with relatively low patient numbers per subgroup - due to rigid selection criteria - make the execution of RCTs of considerable power problematic. To include a sufficient number of patients, TBI trials generally

suffer from a considerable lag time between inception of the study and publication of results. This leads to high costs with a low yield of effect.

Besides these general methodological difficulties in TBI RCTs, specific additional constraints for surgical RCTs exist. Randomizing surgical treatments for TBI may be problematic because of ethical concerns of withholding a potentially lifesaving procedure. Although evidence is lacking, treating surgeons often do not have doubts about the "best" treatment. In case this treatment is surgery, a decision to randomize the patient and obtain informed consent is difficult to execute in the acute phase. And even if a trial succeeds it frequently has limited external validity since the treatment effect has been evaluated in selected populations, with prescriptive management protocols that are sometimes difficult to replicate in the real-world clinical setting.

Several studies have recently been conducted, or are still on-going that address several clinical uncertainties in neurosurgical decision-making (table). No RCTs have been published on the surgical treatment of TBI, until recently, the Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury (DECRA) study was published.[19] In the DECRA trial, the investigators wanted to assess whether early/neuroprotective bifrontal DC can lead to better outcomes compared to standard ICU treatment for patients with diffuse TBI. At 6-month follow-up, a higher rate of unfavorable outcomes was observed in the DC group (OR 2.21; 95% CI 1.14–4.26; p = 0.02). However, 27% of patients in the DC arm had bilaterally unreactive pupils compared with only 12% in the medical arm. Following post-hoc adjustment for pupil reactivity at baseline, the between-group difference in terms of unfavorable outcome was no longer significant (adjusted OR 1.90; 95% CI 0.95–3.79).

Contrary to DECRA, the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-cranial Pressure (RESCUEicp) trial aims to assess the effectiveness of DC as a last-tier therapy for patients with refractory intracranial hypertension. The results (primary end point) are expected in late 2014.

Another surgical study is the Surgical Trial in Traumatic Intracerebral Haemorrhage (STITCH-Trauma), an international multicenter pragmatic randomized controlled trial exploring the value of surgery in patients with intracerebral hemorrhage and contusion. This study inclusion is based on clinical equipoise: only patients for whom the responsible neurosurgeon is uncertain about the benefits of either treatment are eligible. The study started in October 2009 but was halted due to concerns regarding the numbers of patients recruited in the UK. On analysis, a strong tendency towards benefit of early surgery was found, but non-significant due to low numbers.

Table. Recent and emerging studies on surgery for TBI

	Patients	Intervention	Controls	Outcome	Main findings
DECRA	Patients with diffuse TBI within 72 hours post-injury	(Early) secondary (Bifrontal) DC	Standardized ICU treatment	GOSE at 6 months post-injury	- DC greater risk of unfavorable outcome (OR 2.21) - No significant difference in unfavorable outcome (a composite death, vegetative state or severe disability) after post-hoc adjustment for pupil reactivity
RESCUE-ICP	Patients with refractory ICP	(Last resort) secondary DC (hemicraniectomy or bifrontal)	Standardized ICU treatment	-Outcome at discharge (GOS) - GOSE at 6 months post-injury	- Recruitment completed - Follow-up ongoing
STITCH-trauma	- Patients with intracerebral hematoma/ contusion - Based on equipoise of neurosurgeon	Early evacuation of the hematoma	Best medical treatment combined with delayed evacuation (if appropriate)	A prognosis based GOSE/ Modified Rankin Scale	- Halted - Non-significant benefit on primary efficacy analysis
CENTER-TBI/Net-QuRe	Patients with ASDH and/or intracerebral hematoma/ contusion	Non-experimental CER design: - Direct evacuation of the hematoma vs conservative management - Primary DC with evacuation of hematoma vs craniotomy with evacuation of hematoma		GOSE at 6 months post-injury	- Initiated 1st January 2015
RESCUE-ASDH	Patients GCS < 8 with ASDH	Primary DC with evacuation of hematoma	Craniotomy with evacuation of hematoma (only)	GOSE at 12 months post-injury	- Initiated September 2014

CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in TBI; DECRA, Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury; RESCUE-icp, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-cranial Pressure; STITCH-trauma, Surgical Trial in Traumatic Intracerebral Haemorrhage; Net-QuRe, Dutch Neurotraumatology Quality Registry; CER, comparative effectiveness research; RESCUE-ASDH, Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma; DC, decompressive craniectomy; ICU, intensive care unit; ICP, intracranial pressure; GOS, Glasgow Outcome Scale.

FUTURE PERSPECTIVES - COMPARATIVE EFFECTIVENESS RESEARCH

Clearly, there is a need for stronger evidence in the field of surgical treatment of TBI. Future studies in surgical strategies for TBI should focus on feasibility and generalizability, typical characteristics of comparative effectiveness research (CER).[20,21] Non-experimental CER, uses variability in treatment for comparison in real-world conditions and is increasingly used in medicine to compare the outcomes of different treatments.

This approach may allow us to link documented variation in surgical strategies to outcome variation in two promising studies now under development (Table). Specifically, for surgical strategies, the proven variation in surgical strategies will be linked to the outcome variation. Thereby, in CENTER-TBI, we expect to answer the burning clinical questions of this chapters' title: who to operate and when in certain subgroup of patients with ASDH and/or contusions. In addition, the Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH) is an international multicenter, pragmatic, parallel group randomized trial of primary DC versus craniotomy for adult head-injured patients with an ASDH.[22] The new study is currently in the set-up phase and the internal pilot phase is expected to start in 2014.

With these innovative studies as forerunners, we strongly believe that the CER approach has the potential to create more clarity in the uncertainties in the neurosurgical treatment of TBI.[20,21]

Thus, confronted with a patient with TBI, neurosurgeons have to deal with multiple clinical and radiological variables, in a limited time frame and with a shortage of data or predictive outcomes, leading to a broad variation in current practice. We strongly believe that CER approaches and pragmatic trials have potential to create more clarity in the uncertainties in the neurosurgical treatment of TBI.[20,21]

REFERENCES

1. Bullock MR, Chesnut R, Ghajar J, et al. Introduction. *Neurosurgery* 2006;58(Supplement):S2–1–S2–3.
2. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *The Lancet* 2012;380(9847):1088–98.
3. Timofeev I, Dahyot-Fizelier C, Keong N, et al. Ventriculostomy for control of raised ICP in acute traumatic brain injury. *Acta Neurochir Suppl* 2008;102:99–104.
4. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005;1183–92.
5. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006;58(3 Suppl):S16–24–discussionSi–iv.
6. Leitgeb J, Mauritz W, Brazinova A, et al. Outcome after severe brain trauma due to acute subdural hematoma. *Journal of Neurosurgery* 2012;117(2):324–33.
7. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006;58(3 Suppl):S25–46–discussionSi–iv.
8. Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. *Journal of Neurosurgery* 2010;113(3):556–63.
9. Seelig JM, Becker DP, Miller JD, Greenberg RP, Ward JD, Choi SC. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981;304(25):1511–8.
10. Tallon JM, Ackroyd-Stolarz S, Karim SA, Clarke DB. The epidemiology of surgically treated acute subdural and epidural hematomas in patients with head injuries: a population-based study. *Can J Surg* 2008;51(5):339–45.
11. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012;154(9):1555–61.
12. Nijboer JMM, van der Naalt J, Duis ten H-J. Patients beyond salvation? Various categories of trauma patients with a minimal Glasgow Coma Score. *Injury* 2010;41(1):52–7.
13. Dent DL, Croce MA, Menke PG, et al. Prognostic factors after acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1995;39(1):36–42–discussion42–3.
14. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993;121(3-4):100–8.
15. Servadei F, Nasi MT, Cremonini AM, Giuliani G, Cenni P, Nanni A. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998;44(5):868–73.
16. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. *Acta Neurochir* 1999;141(3):223–36.
17. Kolias AG, Belli A, Li LM, et al. Primary decompressive craniectomy for acute subdural haematomas: results of an international survey. *Acta Neurochir* 2012;154(9):1563–5.
18. Maas AIR, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics* 2010;7(1):115–26.
19. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. *N Engl J Med* 2011;364(16):1493–502.
20. Maas AIR, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-Orientation of Clinical Research in Traumatic Brain Injury: Report of an International Workshop on Comparative Effectiveness Research. *Journal of Neurotrauma* 2012;29(1):32–46.
21. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurgical FOCUS* 2012;33(1):E3.
22. Kolias AG, Kirkpatrick PJ, Hutchinson PJ. Decompressive craniectomy: past, present and future. *Nat Rev Neurol* 2013;9(7):405–15.

Chapter 3

The mortality reduction of acute surgery in traumatic acute subdural hematoma since the 19th century: systematic review and meta-analysis with dramatic effect - is surgery the obvious parachute?

Van Essen TA, Res LCS, Schoones JW, de Ruiter GCW, Dekkers OM, Maas A, Peul WC, van der Gaag NA.

J Neurotrauma. 2023 Jan;40(1-2):22-32.

Portions of this work were presented at the 12th Symposium of the International Neurotrauma Society, Capetown, South-Africa, February 1-4, 2016.

ABSTRACT

The rationale of performing surgery for ASDH to reduce mortality is often compared to the self-evident effectiveness of a parachute when skydiving. Nevertheless, it is of clinical relevance to estimate the magnitude of the effectiveness of surgery. The aim of this study is to determine whether surgery reduces mortality in traumatic acute subdural hematoma (ASDH) as compared to initial conservative treatment.

A systematic search was performed in the databases IndexCAT, PubMed, Embase, Web of Science, Cochrane library, CENTRAL, Academic Search Premier, Google Scholar, ScienceDirect, and CINAHL for studies investigating ASDH treated conservatively and surgically, without restriction to publication date, describing the mortality. Cohort studies or trials with at least five patients with ASDH, clearly describing surgical, conservative treatment or both, with the mortality at discharge, reported in English or Dutch, were eligible.

The search yielded 2025 reports of which 282 were considered for full-text review. After risk of bias assessment, we included 102 studies comprising 12,287 patients. The data was synthesized using meta-analysis of absolute risks was conducted in random-effects models, with dramatic effect estimation in subgroups.

Overall mortality in surgically treated ASDH is 48% (95% CI 44-53%). Mortality after surgery for comatose patients (GCS ≤ 8) is 41% (95% CI 31-51%) in contemporary series (after 2000). Mortality after surgery for non-comatose ASDH is 12% (95% CI 4-23%). Conservative treatment is associated with an overall mortality of 35% (95% CI 22-48%), and 81% (95% CI 56-98%) when restricting to comatose patients. The absolute risk reduction (ARR) is 40% (95% CI 35-45%), with a number needed to treat of 2.5 (95% CI 2.2-2.9) to prevent one death in comatose ASDH.

Thus, surgery is effective to reduce mortality among comatose ASDH patients. The magnitude of the effect is large, although the effect size may not be sufficient to overcome any bias.

INTRODUCTION

Three hundred per 100000 people are admitted with traumatic brain injury (TBI) yearly.[1] Of those, 20% has an acute subdural hematoma (ASDH), which is one of the most important causes of the high mortality and substantial morbidity in TBI.[2] Surgical evacuation is considered the cornerstone of treatment but associated with strong practice variation.[3] The evidence level of the effect of surgical evacuation does not rise above class III (Brain Trauma Foundation (BTF) classification of evidence[4]), and is mainly based on uncontrolled cohorts or case series.[2] A systematic review with or without meta-analysis has never been performed. The most recent review is from 1997 and was not performed systematically.[5]

Neurosurgical interventions are seldom based on level I/II evidence.[6] There is a lack of comparative studies that are properly designed to estimate the effectiveness of surgery. In ASDH, neurosurgeons are reluctant to randomize surgery.[7] It is considered unethical because it potentially withholds a lifesaving treatment and common sense can be applied to deduce its effectiveness. Some make the analogy with the effect of a parachute when jumping from a plane.[8]

In an effort to integrate obvious effects with evidence based medicine (EBM), Glasziou et al. coined the term 'dramatic effect' and explored methods to infer causality of several interventions.[9] This approach has also been applied in neurosurgery. The effect of surgery in epidural hematoma (EDH) was determined in a meta-analysis using a historical control group.[10] The Oxford Centre for Evidence Based Medicine has proposed to upgrade observational studies with a dramatic effect to a higher evidence level.[11] Whether surgery for ASDH can be seen as a dramatic effect for which bias is unlikely to explain its apparent effect, remains to be determined.

The question of this study is whether a surgical strategy (i.e. evacuation by craniotomy [CR] or decompressive craniectomy [DC]) leads to lower in-hospital mortality as compared to (initial) conservative treatment in ASDH. Our hypothesis is that mortality in comatose (Glasgow Coma Scale [GCS] ≤ 8) ASDH is high for conservative treatment and much lower for surgery. A large difference between mortality risks, in combination with an endpoint that is not prone to misclassification, would provide robust evidence for which the common sense parachute analogy applies.[10,12] The underlying concept is that the effect will probably be very large and thereby outweighs any practically conceivable bias.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed.[13] The review protocol was preregistered on PROSPERO (registration number CRD42015025491). It was prepared as start of a living systematic review

(LSR) of the CENTER-TBI project (www.center-tbi.eu).[14] The LSR was performed separately, with the Glasgow Outcome Scale (Extended) as outcome and was started in 2016 (PROSPERO CRD42019125336).

Search strategy and selection criteria

To find studies on mortality risks in surgical and conservative ASDH, we searched English and Dutch publications in the databases IndexCAT, PubMed, Embase (OVID-version), Web of Science, Cochrane library, CENTRAL, Academic Search Premier, Google Scholar, ScienceDirect, and CINAHL. The search string focused on traumatic ASDH, cranial surgery, conservative management and outcome, and was devised with a trained librarian (JS). We did not restrict the search to a publication date, as reports on the natural history of ASDH were estimated to be mostly available in very old literature. The search dates from September 19, 2019 (supplemental material 1). For studies describing cohorts with either treatment strategy only, we truncated the search at 2016. The LSR started in 2016 and focused on traditional meta-analysis to infer effectiveness. Therefore, from 2016 onwards we only included studies with both treatment groups.

Original studies were eligible if they met the following criteria: (1) a cohort study or a trial with at least five patients with traumatic ASDH, clearly describing surgical, conservative treatment or both with (2) description of the in-hospital mortality. Studies with patients younger than 16 or with posterior fossa- or interhemispheric ASDH were excluded. Case series were not considered because these do not allow calculation of absolute risks.[15] Studies with outcome-based sampling, for example in studies that diagnose ASDH post-mortem, will be excluded. We included studies with exposure (surgical or conservative treatment) based sampling.

The citations were downloaded into Covidence (www.covidence.org). The initial study selection on abstract and title was independently done by two authors (TvE, NvdG). Full texts were reviewed by three authors (TvE, LR, NvdG). Discrepancies were solved by consensus. We did not treat the absence of a stated aim, an unclear aim, or an aim discordant from our systematic review, as exclusion factors.

Definitions

We used the BTF's definition of ASDH: every patient within 2 weeks of head injury and a diagnosis of a subdural localized hematoma (either on CT, by angiography, by other radiological exams (including air ventriculography) and/or by surgery).[2] Subacute or chronic subdural hematomas were not considered.

Pragmatic definitions for a primary surgical and conservative treatment strategy were used by adhering to the definition of the study in question. However, a surgical strategy had to include at least: (1) a CR or a DC to evacuate the hematoma and (2)

initiated within 24 hours of presentation or, when no time window was reported, surgery directly after the first CT that revealed the ASDH. A conservative strategy is any hospital admittance with associated medical interventions without a CR or a DC within 24 hours of presentation or after the first CT with optional secondary CR or DC in case of secondary deterioration after 24 hours.

Because the presentation of ASDH is clinically heterogeneous, we regarded several outcome predictors relevant:

- Clinical parameters: age, level of consciousness as an indicator of TBI severity (mild and moderate (GCS > 8), mixed, severe (GCS ≤ 8)), pupillary reactivity (abnormal or non-reactive to light, normal);
- Radiological parameters: thickness of the ASDH, the severity of midline shift, other intracranial lesions (e.g. contusions);
- Process parameters: time to hospital, time to operation (either from injury or from hospital).

If two out of three parameters were completely described, the article was qualified as adequately reporting relevant prognostic characteristics.

Data extraction and risk of bias assessment

Data was independently extracted by two authors (LR, TvE). Discrepancies were resolved by consensus. The following data were extracted: study design, presence of a comparison group, sample size, in-hospital mortality, inclusion and exclusion criteria, age, GCS, anti-coagulant use, concomitant intracranial hematoma/contusion, proportion surgically treated (in case of comparative studies), operation type (DC, CR and/or BR), report on relevant outcome predictors, and CT diagnose of ASDH. Further, we extracted whether the cohort of patients consisted of a subpopulation.

Risk of bias was assessed by an adapted MINORS instrument.[16] The 'low risk of bias'-requirements were: (a) ascertainment of exposure by CT, (b) consecutive inclusion, (c) prospective data collection, and (d) adequate description of prognostic characteristics (see 'Definitions'). In (comparative) studies containing both treatment groups, additional criteria for 'low risk of bias' were: (e) contemporary groups (no historical comparison), (f) baseline equivalence of groups, and (g) adequate adjustment for confounders. At the end of this process we allocated each study to a dichotomic qualitative score 'low risk of bias' 'yes' or 'no', instead of the original quantification of the risk of bias from MINORS, because numerical representation of the components may be misleading.[17]

Statistical analysis

The pooled mortality risk (proportion) was the outcome measure. Mortality was stratified on publication date (before vs after CT-era), age categories, and presenting

consciousness level (motor score 6/GCS > 8 versus motor score < 6/GCS ≤ 8). After assessment of risk of bias and study heterogeneity, pooled estimates of respectively the proportions of the surgical and conservative cohorts and of the effect measures (i.e. relative risks, odds ratios) from the comparative studies were obtained. The predefined plan for meta-analyses:

The first strategy assumed a dramatic effect (of surgery on mortality) by comparison with estimations from historical cohorts. The assumptions are 1) an objective outcome measure, not prone to misclassification, 2) a high mortality risk in untreated subjects confirmed by multiple cohorts and 3) a much lower mortality risk in surgically treated subjects in multiple cohorts. The pooled mortality risk of the surgical cohorts was compared to that of the conservative cohorts by use of the absolute risk reduction (ARR), relative risk (RR) and the numbers-needed-to-treat (NNT) to quantify the effect of surgery on mortality.[10] We sought to provide these effect measures specifically for the comatose subgroup (GCS ≤ 8) in which the dramatic effect assumptions apply. In this analysis, we compared mortality in surgery cohorts after 2000 with mortality in all conservative cohorts. Thereby aiming for an accurate reflection of modern-day surgery and an appropriate estimate of conservative treatment of comatose ASDH respectively. Sensitivity analyses were performed with and without restricting to time period (after 2000).

The second strategy was a (conventional) meta-analysis with pooling of effect estimates. Pooled estimates were obtained when studies were termed low risk of bias.

Meta-analyses for effect estimates and for proportions were carried out using the *metan* and *metaprop* commands[18,19] in Stata 14 (Stata Corp., College Station, TX, USA) in random-effects models.

RESULTS

Study Characteristics

One hundred and two studies were included involving data from 12,287 patients (Fig. 1): seventy cohort studies of surgically treated ASDH, 11 cohort studies of natural history/conservatively treated ASDH and 21 studies containing both surgically and conservatively treated patients (Table 1, 2, 3 in supplemental material 2).[20-121] Consequently, there were 91 surgical cohorts and 32 conservative cohorts of which the natural history of ASDH can be inferred. All studies considered, mortality was 46% (95% CI 42-51%).

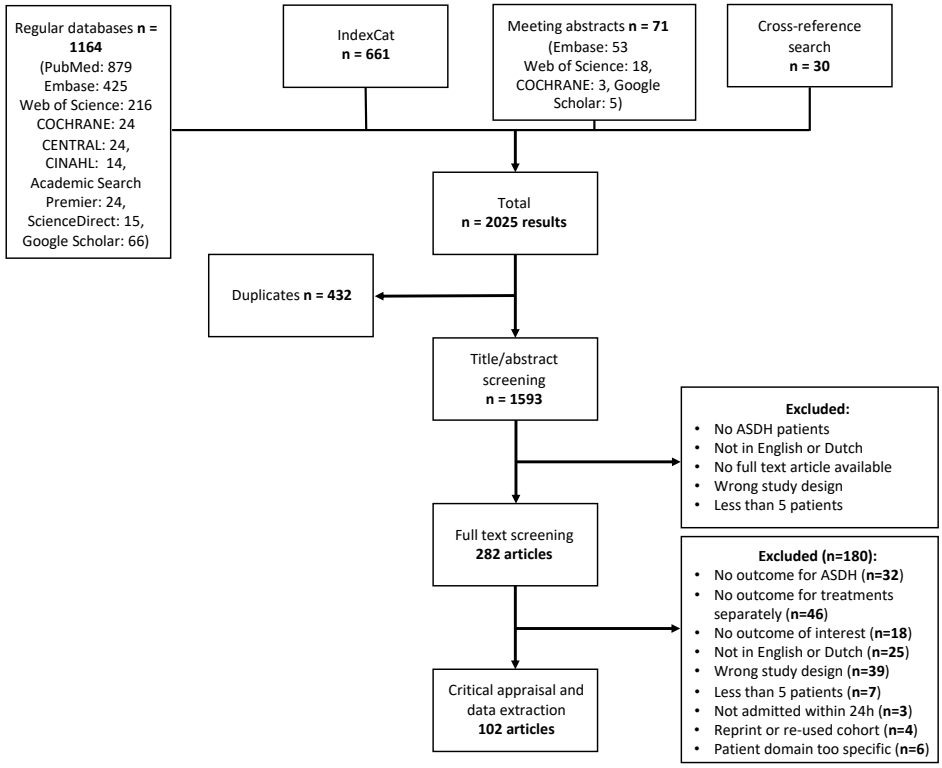


Figure 1. Flow diagram of screened, included and excluded studies.

Risk of bias and heterogeneity

Four of the conservative cohorts (13%) had a low risk of bias compared to eight surgical cohorts (9%) (Table 1, 2 and 4 in supplemental material 2). None of the studies containing both groups, had a low risk of bias (Table 3 and 4 in supplemental material 2). Visual (qualitative) assessment of the wide variability in the reported mortality risks of the studies in the forest plots showed substantial between-study heterogeneity.

Mortality in surgically treated acute subdural hematoma patients

The overall mortality in the surgery group was 48% (95% CI 45-52%). Patients younger than 30 and older than 60 had a lower mortality (respectively 19% and 31%) than patients between 30 and 60 years (44% and 54% respectively for 31-45 and 46-60 years, Fig. 1 in supplemental material 2).

There were two surgical cohorts for non-comatose ASDH. In these studies patients had a GCS between 11-15 and the pooled mortality was 12% (95% CI 4-23%). Thirty-

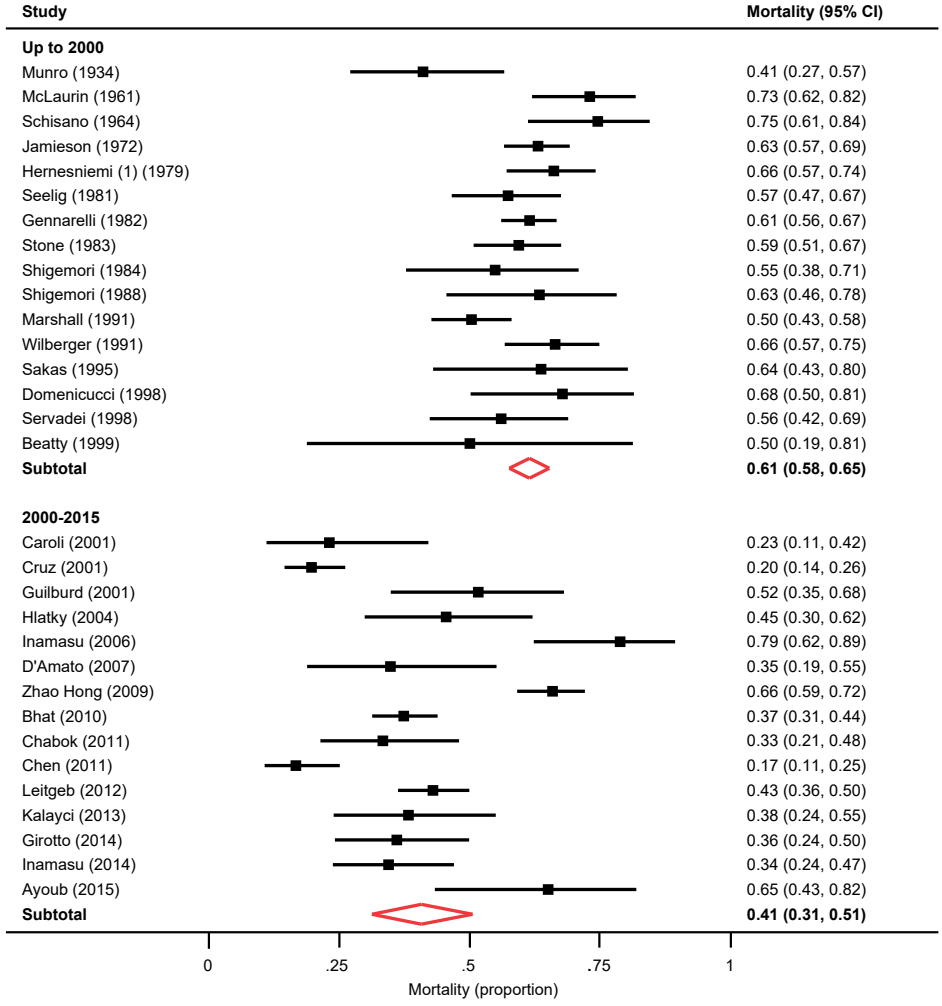


Figure 2. Historical and contemporary mortality risks in surgically treated comatose acute subdural hematoma patients.

The squares and horizontal lines correspond to the mortality risks with 95% CIs. The diamond represents the pooled mortality risk and 95% CI of the subgroup population.

one studies in comatose ASDH patients showed a pooled mortality of 51%, 95% CI 45-58 (Fig. 2 in supplemental material 2). Pooled mortality for (surgical) ASDH in studies without restriction to TBI severity (i.e. GCS 3-15) was 45% (95% CI 38-51, Fig. 3 in supplemental material 2).

Mortality before the CT-era was 59% and in studies with a CT diagnosis of ASDH mortality was 45% (Fig. 4 in supplemental material 2). Surgery for comatose ASDH

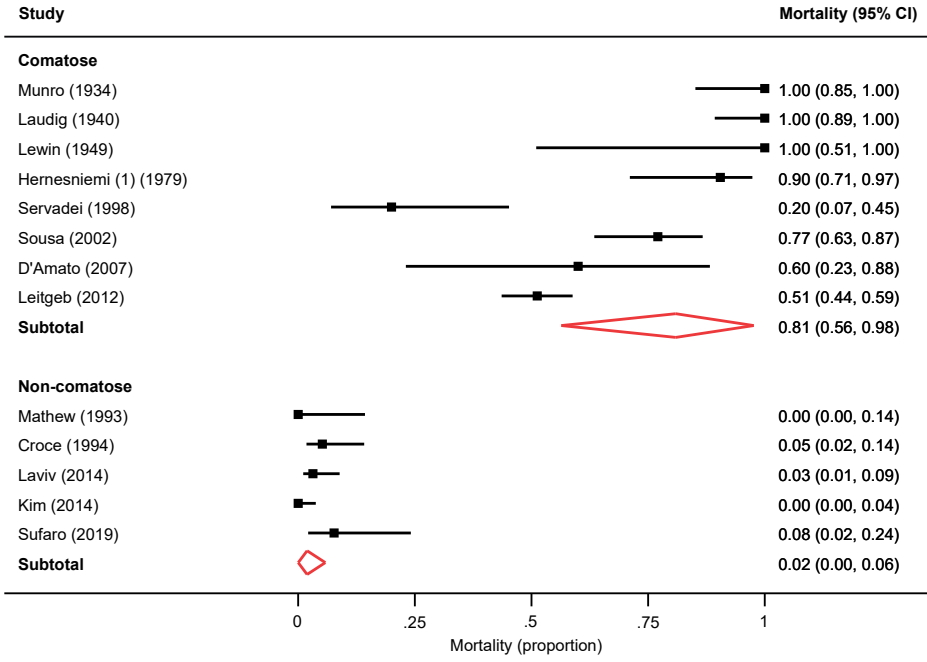


Figure 3. Mortality of the natural history or conservative treatment of comatose and non-comatose acute subdural hematoma patients.

The squares and horizontal lines correspond to the mortality risks with 95% CIs. The diamond represents the pooled mortality risk and 95% CI of the subgroup population.

patients in more recent studies (after 2000) is associated with a pooled mortality of 41% while mortality was 61% in studies before 2000 (Fig. 2).

Mortality after conservative treatment of acute subdural hematoma

The overall mortality risk after conservative treatment was 35% (95% CI 22-48%), inferred from studies describing the natural history of ASDH and studies of conservatively treated comatose ASDH. Pooling comatose ASDH patients with conservative treatment, resulted in a mortality of 81% (95% CI 56-98%, Fig. 3), while in studies after 2000, conservative treatment is associated with a pooled mortality of 64% (95% CI 41-81%). Pooled mortality in conservative treated non-comatose ASDH patients was 2% (95% CI 0-6%, Figure 3). Pooled mortality of ASDH conservative management in mixed GCS cohorts was 26% (95% CI 13-40%, Fig. 5 in supplemental material 2).

Table 1. Summary statistics of the effect measures of surgery for acute subdural hematoma

	Treatment for ASDH (95% CI, number of studies)
Mortality without intervention	81% (56-98, n = 8)
Mortality with intervention	41% (31-51, n = 15)
ARR	40% (31-49)
RRR	49%
NNT	2.5 (2.0-3.2)

ASDH: acute subdural hematoma. ARR (absolute risk reduction). CI (confidence interval). RRR (relative risk reduction). NNT (number needed to treat).

Table 2. Summary statistics of the effect measures of surgery for epidural hematoma and parachute in free-fall

	Surgery for EDH*	Parachute in free-fall*
Mortality without intervention	99% (95-99)	74% (69-79)
Mortality with intervention	13% (11-15)	0% (0.0011-0.0017)
ARR	86% (82-89)	74% (69-79)
RRR	87%	99.9%
NNT	1.2 (1.1-1.2)	1.4 (1.3-1.5)

EDH: epidural hematoma. ARR (absolute risk reduction). RRR (relative risk reduction). NNT (number needed to treat).
* Adapted from [10].

Treatment effect

The absence of studies with a low risk of bias as well as the considerable between-study heterogeneity, as can be inferred from the widely varying mortality risks, do not allow meta-analysis of effect estimates. Moreover, among the studies with both cohorts, there were no comparative studies that presented effect measures.

The mortality risk associated with the conservative treatment of comatose ASDH patients, was 81% (Fig. 3). Compared to the mortality of modern surgery in comatose ASDH patients of 41%, this translates to an ARR 40% and a NNT of 2.5 (Table 1).

Restricting the historical control group to after 2000 as well, leads to an ARR of 23% (95% CI 13-32%) and a NNT of 4.3 (3.1-7.7). And finally, without restricting to time period leads to 81 versus 51% with an ARR of 30% (95% CI 24-36%) and a NNT of 3.3 (2.8-4.2).

DISCUSSION

ASDH is associated with poor outcome despite surgery. Mortality in surgically treated comatose patients has been reduced considerably since the 19th century. Surgery is nowadays associated with a mortality of 41%. In historical cohorts, conservatively treated ASDH has a mortality of 81%. Together this leads to an ARR 40% and a NNT of 2.5. In clinically relatively good patients (GCS 9-15) there is no obvious mortality benefit of surgery.

We assumed a strong effect of surgery to determine the relation of surgery and mortality in ASDH. The validity of our conclusion relies on whether our effect is dramatic enough that confounding and immortal time bias can be sufficiently ruled out. The magnitude of the effect is large, although not as large as surgery for EDH (ARR 74%) or as for a parachute when skydiving (ARR 86%, Table 2). ASDH is a more debilitating disease than EDH because of underlying primary brain damage, and even after (modern-day) surgery the mortality is high. Glasziou et al and Nelson et al. propose a risk ratio (RR) of at least 10 and an ARR of 50% respectively, to qualify as a convincing difference to claim a treatment effect.[9,10] Even when the mortality of the natural history of ASDH would be 100%, these dramatic effect thresholds would not be reached with a RR of 2.4 and an ARR of 59%. According to these conventions, surgery for ASDH would qualify but with low confidence.

The type of control group influences the effect size. When restricting the conservative treatment estimate to after 2000, the ARR was 23%. This difference is not considered a dramatic effect beyond doubt and can be explained by bias. However, the clinical decision for conservative treatment in these three studies was (well) reasoned, i.e. strong confounding by indication, resulting in a selected subgroup (not neurologically deteriorating patients with small ASDH and normal ICP). This control group is therefore less appropriate. The type of control group requires balancing between an accurate reflection of curative ability of conservative management against highly selected populations of comatose patients amenable to conservative management. By including studies done before the widespread use of CT, we are exploiting the pre-CT era's inability to fully appreciate the strong curative potential of surgical evacuation. By combining those with modern conservative cohorts, we aimed to obtain an accurate reflection of conservative treatment mortality risk of comatose ASDH.

Is this study a mere exercise in epidemiological theory and unnecessary complex rendition of common sense? In other words, what are the implications of our results? First, our results demonstrate that surgical evacuation of ASDH is an effective intervention. TBI guidelines should reflect the consensus that observational studies with a dramatic effect should be regarded as level-2 evidence, similar to randomized trials.[11] It may be argued that there is no need for additional study into the effect of

surgery in comatose patients in terms of mortality reduction, especially for the rapidly deteriorating young patient with one nonreactive pupil and an isolated ASDH. On the other hand, the question may be raised whether the results are sufficient not to perform a randomized trial. The ARR of 40% could be considered not a dramatic effect beyond doubt. It might be explained by confounding, selection bias and immortal time bias. Although ASDH is seen as a progressive condition with a certain death, it probably should be seen as spontaneous remitting. In contrast to EDH, ASDH is often of venous origin instead of arterial, perhaps making a good clinical outcome possible after expectant management. After all, chronic subdural hematoma arise from liquefication of an ASDH – albeit without or little symptoms mostly. Some of the included studies confirm this satisfactory prognosis of conservative treatment of comatose ASDH patients. Thus, at least in certain comatose ASDH subgroups randomized trials are defendable.

Second, this study does not support the notion that older patients have a worse outcome. A possible explanation, though, could be selection bias where older patients are deceased before hospital admission and therefore not included in any study. However, the current results are in line with clinical experience that older patients often have an isolated ASDH without contusion as a result of a low energetic head trauma that may respond well to an early evacuation with a small craniotomy or conservative treatment with watchful waiting and eventually a delayed burr hole drainage.

Third, this study highlights the improved care for patients with ASDH over the past century. The targeted and efficient craniotomy and DC to treat severe TBI and ASDH have coincided with the evolution of trauma care systems. Advances in neurocritical care and the widespread introduction of CT-scanners and ICP monitors, have decreased mortality for patients with severe TBI dramatically in modern well-resourced hospitals.

Fourth and final, the effect of surgery in moderate TBI could not be estimated because cohorts restricting to moderate TBI were not available. However, the probable positive effect exerts its influence mostly in terms of functional outcome since the in-hospital mortality of conservatively treated non-comatose ASDH already is relatively low with 2%.

This is the first systematic review of ASDH surgery. A strength is that it profits from an exhaustive search of ASDH studies with an overview spanning 120 years ASDH care. Limitations are the restriction to mortality as outcome and the broad eligibility criteria, leading to strong between-study heterogeneity. Furthermore, the study may have suffered from (positively skewed) publication bias. ASDH is associated with poor outcome which can lead to under-publication of cohorts with a less favorable outcome.

This report provides a reference for studies into the effectiveness of surgery for ASDH. Apart from surgery for comatose ASDH in terms of mortality, surgery in ASDH is of unclear benefit. Wide practice variation confirms this statement.[7,122] Subgroups such as patients with moderate TBI and the elderly warrant high-quality comparative studies. In addition, the effect of surgery on functional outcome and quality of life requires further investigation.

Conclusion

By comparing contemporary surgical treatment with the natural history of ASDH in a systematic review of the mortality risk, surgery seems to reduce mortality among comatose ASDH patients almost twofold. This finding integrates common sense, i.e. obvious effects, with EBM standards, although the effect size may not be sufficient to overcome any bias.

Acknowledgments

We like to thank Kyle S. Nelson, Ann M. Brearley and Stephen J. Haines for their study *Evidence-based assessment of well-established interventions: the parachute and the epidural hematoma* (Neurosurgery 2014;75:552–9) that served as an inspiration for the current study.

Portions of this work were presented orally as a plenary lecture at the European Association of Neurosurgical Societies (EANS) congress, Dublin, Ireland, in 2019.

Authors' Contributions

Authors TvE and NG conceived and designed the review. The literature search was devised by TvE and JS. TvE and LR performed study screening for inclusion, data extraction, assessment of risk of bias, and selection of studies for inclusion in meta-analyses. Full texts were reviewed by three authors (TvE, LR, NvdG) and any disagreements were settled by these same authors. Analysis of the data was performed by TvE and LR. All authors contributed to the review protocol, methodological decisions and manuscript.

Transparency, Rigor and Reproducibility Summary

The data, which include individual study data, a database with a data dictionary defining each field and the Stata syntax, are available upon reasonable request. The predefined study protocol has been published (PROSPERO [registration number CRD42015025491])

Funding Information

The authors' work on this study is funded by the Hersenstichting Nederland (the Dutch Brain Foundation, grant number ps2014.06) for the Dutch Neurotraumatology Quality Registry (Net-QuRe) and the European Union seventh Framework Program (grant 602150) for CENTER-TBI.

Author Disclosure Statement

The authors have no competing interests with regard to this article.

Supplemental material available online: https://www.liebertpub.com/doi/10.1089/neu.2022.0137

Supplemental material 1. Search strategy and output

Supplemental material 2. Supplemental tables and figures

REFERENCES

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12):987-1048.
2. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; 58(3 Suppl): S16–24–discussionSi–iv.
3. Van Essen TA, de Ruiter GCW, Kho KH, et al. Neurosurgical treatment variation of traumatic brain injury - Evaluation of acute subdural hematoma management in Belgium and The Netherlands. *Journal of Neurotrauma* 2016; neu.2016.4495.
4. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; 58(3 Suppl):S16–24–discussionSi–iv.
5. Servadei F. Prognostic factors in severely head injured adult patients with acute subdural haematoma's. *Acta Neurochir* 1997; 139(4):279-285.
6. Yarascavitch BA, Chuback JE, Almenawer SA, et al. Levels of Evidence in the Neurosurgical Literature. *Neurosurgery* 2012; 71(6):1131-1138;
7. Van Essen TA, de Ruiter GCW, Kho KH, et al. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *Journal of Neurotrauma* 2017; 34(4):881-889; doi:10.1089/neu.2016.4495.
8. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005: 1183-1192.
9. Glasziou P, Chalmers I, Rawlins M, et al. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007; 334(7589):349-351.
10. Nelson KS, Brearley AM, Haines SJ. Evidence-based assessment of well-established interventions: the parachute and the epidural hematoma. *Neurosurgery* 2014; 75(5):552–9–discussion559;
11. Howick J, Library ICJL, Glasziou P, et al. "The Oxford Levels of Evidence 2." Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653.
12. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327(7429):1459-1461.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372; doi:10.1136/bmj.n71.
14. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; 76(1):67-80.
15. Dekkers OM, Egger M, Altman DG, et al. Distinguishing case series from cohort studies. *Ann Intern Med* 2012; 156(1 Pt 1):37-40;
16. Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; 73(9):712-716.
17. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *American Journal of Epidemiology* 1994; 140(3):290-296;
18. Harris R, Bradburn M, Deeks J, et al. metan: fixed- and random-effects meta-analysis. *Stata Journal* 2008; 8(1):3-28.
19. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Archives of Public Health* 2014; 72:39.
20. Bowen WH. Traumatic Subdural Hemorrhage. *Guys Hosp Rep* 1905;(59):21.
21. Coleman CC. Intracranial Hemorrhage Following Head Injury. *Southern Medical Journal* 1928; (9):697.
22. Munro D. The diagnosis and treatment of subdural hematoma. *N Engl J Med* 1934; 210(22):1-16.
23. Kennedy F, Wortis H. Acute epidural and subdural hematomas. *Tr Am Neur Ass* 1936; (62):22-24.
24. Laudig GH, Browder EJ, Watson RA. Subdural Hematoma: A Study Of One Hundred Forty-Three Cases Encountered During A Five-Year Period. *Annals of Surgery* 1941; 113(2):170-191.
25. Lewin W. Acute Subdural and Extradural Haematoma in Closed Head Injuries. *Annals of the Royal College of Surgeons of England* 1949; 5(4):240-274.
26. McLaurin RL, Tutor FT. Acute Subdural Hematoma. *Journal of Neurosurgery* 1961 18(1):61-67.
27. Schisano G, Burzaco J. Acute And Subacute Subdural Haematomas. *Acta Chir Scand* 1964; 128:471-482.
28. Moiel Rh, Caram Pc. Acute Subdural Hematomas: A Review of Eighty-Four

Cases, A Six Year Evaluation. *J Trauma Acute Care Surg* 1967;7 N2 -(5).
29. Gutterman P, Shenkin HA. Prognostic features in recovery from traumatic decerebration. *Journal of Neurosurgery* 1970; 32(3):330-335.
30. Ransohoff J, Benjamin MV, Gage ELJ, et al. Hemicraniectomy in the management of acute subdural hematoma. *Journal of Neurosurgery* 1971; 34(1):70-76.
31. Talalla A, Morin MA. Acute traumatic subdural hematoma: a review of one hundred consecutive cases. *The Journal of Trauma: Injury, Infection, and Critical Care* 1971; 11(9):771-777.
32. Jamieson KG, Yelland JD. Surgically treated traumatic subdural hematomas. *Journal of Neurosurgery* 1972; 37(2):137-149.
33. Tjan TG, de Grood MP. [Acute subdural hematoma]. *Ned Tijdschr Geneeskd* 1973; 117(23):876-880.
34. Fell DA, Fitzgerald S, Moiel RH, et al. Acute subdural hematomas. Review of 144 cases. *Journal of Neurosurgery* 1975; 42(1):37-42.
35. Britt RH, Hamilton RD. Large decompressive craniotomy in the treatment of acute subdural hematoma. *Neurosurgery* 1978; 2(3):195-200;
36. Rosenørn J, Gjerris F. Long-term follow-up review of patients with acute and subacute subdural hematomas. *Journal of Neurosurgery* 1978; 48(3):345-349.
37. Hernesniemi J. Outcome following acute subdural haematoma. *Acta Neurochir* 1979; 49(3-4):191-198.
38. Hernesniemi J. Outcome following head injuries in the aged. *Acta Neurochir* 1979; 49(1-2):67-79.
39. Klun B, Fettich M. Factors determining prognosis in acute subdural haematoma. *Acta Neurochir Suppl (Wien)* 1979; 28(1):134-136.
40. Shigemori M, Syojima K, Nakayama K, et al. The outcome from acute subdural haematoma following decompressive hemicraniectomy. *Acta Neurochir* 1980; 54(1-2):61-69.
41. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304(25):1511-1518.
42. Gennarelli TA, Thibault LE. Biomechanics of acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1982; 22(8):680-686;
43. Shenkin HA. Acute subdural hematoma. Review of 39 consecutive cases with high incidence of cortical artery rupture. *Journal of Neurosurgery* 1982; 57(2):254-257.
44. Stone JL, Rifai MH, Sugar O, et al. Subdural hematomas. I. Acute subdural hematoma: progress in definition, clinical pathology, and therapy. *Surg Neurol* 1983; 19(3):216-231.
45. Yue CP, Mann KS, Ong GB. Acute subdural haematoma: better results with neurosurgeons than general surgeons. *Injury* 1983; 14(6):489-492.
46. Klun B, Fettich M. Factors influencing the outcome in acute subdural haematoma. *Acta Neurochir* 1984; 71(3):171-178.
47. Shigemori M, Yuge T, Tokutomi T, et al. Decompressive hemicraniectomy for acute subdural hematoma. *Kurume Med J* 1984; 31(2):81-87.
48. Turazzi S, Bricolo A, Pasut ML. Review of 1,000 consecutive cases of severe head injury treated before the advent of CT scanning. *Acta Neurochir* 1984; 72(3):167-195.
49. Haselsberger K, Pucher R, Auer LM. Prognosis after acute subdural or epidural haemorrhage. *Acta Neurochir* 1988; 90(3-4):111-116.
50. Shigemori M, Tokutomi T, Yuge T, et al. Surgical treatment of acute subdural hematomas in patients with low Glasgow Coma Scale scores. *Kurume Med J* 1988; 35(1):39-42.
51. Conzen M, Dette M, Antoniadis C, et al. Acute subdural hematoma with and without multiple injuries. *Neurosurgical Review* 1989; 12 Suppl 1:201-206;
52. Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *Journal of Neurosurgery* 1991; 75(Supplement):S14-S20.
53. Wilberger JE, Harris M, Diamond DL. Acute subdural hematoma: morbidity, mortality, and operative timing. *Journal of Neurosurgery* 1991; 74:212-218.
54. Cagetti B, Cossu M, Pau A, et al. The outcome from acute subdural and epidural intracranial haematomas in very elderly patients. *Br J Neurosurg* 1992; 6(3):227-231.
55. Jamjoom A. Justification for evacuating acute subdural haematomas in patients above the age of 75 years. *Injury* 1992; 23(8):518-520.
56. Kotwica Z, Brzeziński J. [Clinical course and the results of the treatment of unilateral chronic subdural hematoma]. *Neurol Neurochir Pol* 1992; Suppl 1:293-299.
57. Lee KS, Bae HG, Yun IG. Small-sized acute subdural hematoma: operate or not. *J Korean Med Sci* 1992; 7(1):52-57.
58. Sonne NM, Tønnesen H. The influence of alcoholism on outcome after evacuation of

subdural haematoma. *Br J Neurosurg* 1992; 6(2):125-130.
59. Hatashita S, Koga N, Hosaka Y, et al. Acute subdural hematoma: severity of injury, surgical intervention, and mortality. *Neurologia Medico-chirurgica* 1993; 33(1):13-18.
60. Kotwica Z, Brzeziński J. Acute subdural haematoma in adults: an analysis of outcome in comatose patients. *Acta Neurochir.* 1993; 121(3):95-99.
61. Phuenpathom N, Choomuang M, Ratanalert S. Outcome and outcome prediction in acute subdural hematoma. *Surg Neurol* 1993; 40(1):22-25.
62. Croce MA, Dent DL, Menke PG, et al. Acute subdural hematoma: nonsurgical management of selected patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1994; 36(6):820–6–discussion826–7.
63. Dent DL, Croce MA, Menke PG, et al. Prognostic factors after acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1995; 39(1):36–42–discussion42–3.
64. Sakas DE, Bullock MR, Teasdale GM. One-year outcome following craniotomy for traumatic hematoma in patients with fixed dilated pupils. *Journal of Neurosurgery* 1995; 82(6):961-965.
65. Massaro F, Lanotte M, Faccani G, et al. One hundred and twenty-seven cases of acute subdural haematoma operated on. Correlation between CT scan findings and outcome. *Acta Neurochir* 1996; 138(2):185-191.
66. Zumkeller M, Behrmann R, Heissler HE, et al. Computed tomographic criteria and survival rate for patients with acute subdural hematoma. *Neurosurgery* 1996; 39(4):708–12–discussion712–3.
67. Koç RK, Akdemir H, Oktem IS, et al. A. Acute subdural hematoma: outcome and outcome prediction. *Neurosurgical review* 1997; 20(4):239-244.
68. Domenicucci M, Strzelecki JW, Delfini R. Acute posttraumatic subdural hematomas: "intradural" computed tomographic appearance as a favorable prognostic factor. *Neurosurgery* 1998; 42(1):51-55.
69. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care*. 1998; 44(5):868-873.
70. Beatty RA. Subdural haematomas in the elderly: experience with treatment by trephine craniotomy and not closing the dura or replacing the bone plate. *Br J Neurosurg* 1999; 13(1):60-64.
71. Caroli M, Locatelli M, Campanella R, et al.. Multiple intracranial lesions in head injury: clinical considerations, prognostic factors, management, and results in 95 patients. *Surg Neurol* 2001; 56(2):82-88.
72. Cruz J, Minoja G, Okuchi K. Improving clinical outcomes from acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. *Neurosurgery* 2001; 49(4):864-871.
73. Guilburd JN, Sviri GE. Role of dural fenestrations in acute subdural hematoma. *Journal of Neurosurgery* 2001; 95(2):263-267.
74. Munro PT, Smith RD, Parke TRJ. Effect of patients' age on management of acute intracranial haematoma: prospective national study. *BMJ* 2002; 325(7371):1001.
75. Hlatky R, Valadka AB, Goodman JC, et al. Evolution of brain tissue injury after evacuation of acute traumatic subdural hematomas. *Neurosurgery* 2004; 55(6):1318–23–discussion1324.
76. Inamasu J, Saito R, Nakamura Y, et al. Therapeutic hypothermia for severely head-injured patients with acute subdural haematoma. *Journal of Clinical Neuroscience* 2006; 13(7):733-737.
77. Woertgen C, Rothoerl RD, Schebesch KM, et al. Comparison of craniotomy and craniectomy in patients with acute subdural haematoma. *Journal of Clinical Neuroscience* 2006;13(7):718-721.
78. D'Amato L, Piazza O, Alliata L, et al. Prognosis of isolated acute post-traumatic subdural haematoma. *Journal of Neurosurgical Sciences* 2007; 51(3):107-111.
79. Tian H-L, Chen S-W, Xu T, et al. Risk factors related to hospital mortality in patients with isolated traumatic acute subdural haematoma: analysis of 308 patients undergone surgery. *Chin Med J (Engl)* 2008; 121(12):1080-1084.
80. Tallon JM, Ackroyd-Stolarz S, et al. The epidemiology of surgically treated acute subdural and epidural hematomas in patients with head injuries: a population-based study. *Can J Surg* 2008; 51(5):339-345.
81. Taussky P, Widmer HR, Takala J, et al. Outcome after acute traumatic subdural and epidural haematoma in Switzerland: a single-centre experience. *Swiss Med Wkly* 2008; 138(19-20):281-285.
82. Hanif S, Abodunde O, Ali Z, et al. Age related outcome in acute subdural haematoma following traumatic head injury. *Ir Med J* 2009; 102(8):255-257.

83. Kim K-H. Predictors for functional recovery and mortality of surgically treated traumatic acute subdural hematomas in 256 patients. *Journal of Korean Neurosurgical Society* 2009; 45(3):143-150.
84. Kushi H, Saito T, Sakagami Y, et al. Acute subdural hematoma because of boxing. *The Journal of Trauma: Injury, Infection, and Critical Care* 2009;66(2):298-303.
85. Senft C, Schuster T, Forster M-T, et al. Management and outcome of patients with acute traumatic subdural hematomas and pre-injury oral anticoagulation therapy. *Neurol Res* 2009;31(10):1012-1018.
86. Zhao H, Bai X-J. Influence of operative timing on prognosis of patients with acute subdural hematoma. *Chin J Traumatol* 2009;12(5):296-298.
87. Bhat AR. Acute subdural hematoma with severe traumatic brain edema evacuated by Dural-stabs -A new brain preserving technique. *Biomedical Research* 2010;21(2):167-173.
88. Cai Y, Zhong X-M, Wang Y-Q, et al. Acute subdural hematoma with swirl signs: clinical analysis of 15 cases. *Chin J Traumatol* 2010;13(4):253-254.
89. Karasu A, Civelek E, Aras Y, et al. Analyses of clinical prognostic factors in operated traumatic acute subdural hematomas. *Ulus Travma Acil Cerrahi Derg* 2010;16(3):233-236.
90. Kiboi JG, Kitunguu PK, Angwenyi PO, et al. Outcome after acute traumatic subdural haematoma in kenya: a single-centre experience. *African Journal of Neurological Sciences* 2010;29(1):38-46.
91. Rabinstein AA, Chung SY, Rudzinski LA, et al. Seizures after evacuation of subdural hematomas: incidence, risk factors, and functional impact. *Journal of Neurosurgery* 2010;112(2):455-460.
92. Chabok S, Safaie M, Dehnadi Moghadam A, et al. Acute Subdural Hematoma: A Comparative Study of 2 Types of Operative Techniques. *Neurosurgery Quarterly* 2011;21:103-106.
93. Chen S-H, Chen Y, Fang W-K, et al. Comparison of craniotomy and decompressive craniectomy in severely head-injured patients with acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 2011;71(6):1632-1636.
94. Panczykowski DM, Okonkwo DO. Premorbid oral antithrombotic therapy and risk for reaccumulation, reoperation, and mortality in acute subdural hematomas. *Journal of Neurosurgery* 2011;114(1):47-52.
95. Tien HCN, Jung V, Pinto R, et al. Reducing time-to-treatment decreases mortality of trauma patients with acute subdural hematoma. *Annals of Surgery* 2011;253(6):1178-1183.
96. Leitgeb J, Mauritz W, Brazinova A, et al. Outcome after severe brain trauma due to acute subdural hematoma. *Journal of Neurosurgery* 2012;117(2):324-333.
97. Leung GKK, Ng GKB, Ho W, et al. Impact of a multidisciplinary trauma team on the outcome of acute subdural haematoma. *Injury* 2012;43(9):1419-1422.
98. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012;154(9):1555-1561.
99. Ryan CG, Thompson RE, Temkin NR, et al. Acute traumatic subdural hematoma: current mortality and functional outcomes in adult patients at a Level I trauma center. *J Trauma Acute Care Surg* 2012;73(5):1348-1354; doi:10.1097/TA.0b013e31826fcb30.
100. Taussky P, Hidalgo ET, Landolt H, et al. Age and salvageability: analysis of outcome of patients older than 65 years undergoing craniotomy for acute traumatic subdural hematoma. *World Neurosurg* 2012;78(3-4):306-311.
101. Kalayci M, Aktunç E, Gül S, et al. Decompressive craniectomy for acute subdural haematoma: an overview of current prognostic factors and a discussion about some novel prognostic parametres. *J Pak Med Assoc* 2013;63(1):38-49.
102. Baraniskin A, Steffens C, Harders A, et al. Impact of pre-hospital antithrombotic medication on the outcome of chronic and acute subdural hematoma. *Journal of Neurological Surgery* Part A, Central European neurosurgery 2014;75(1):31-36.
103. Girotto D, Ledić D, Daji V, et al. Neurosurgical procedure for treatment of traumatic subdural hematoma with severe brain injury: a single center matched-pair analysis. *Coll Antropol* 2014;38(4):1255-1258.
104. Inamasu J, Hasegawa M, Hayashi T, et al. Hemispheric differences in the surgical outcomes of patients with traumatic acute subdural hematoma. *J Negat Results Biomed* 2014;13(1):10.
105. Shimoda K, Maeda T, Tado M, et al. Outcome and Surgical Management for Geriatric Traumatic Brain Injury: Analysis of 888 Cases Registered in the Japan Neurotrauma Data Bank. *World Neurosurg* 2014;82(6):1300-1306.
106. Walcott BP, Khanna A, Kwon C-S, et al. Time interval to surgery and outcomes following the surgical treatment of acute

traumatic subdural hematoma. *Journal of Clinical Neuroscience* 2014;21(12):2107-2111.
107. Ayoub B, Elmallawany M. Comparison of Burr Holes and Decompressive Craniotomy in the Surgical Treatment of Traumatic Acute Subdural Hematoma. *The Medical Journal of Cairo University* 2015. Vol. 83, March
108. Bartels RHMA, Meijer FJA, van der Hoeven H, Edwards M, Prokop M. Midline shift in relation to thickness of traumatic acute subdural hematoma predicts mortality. *BMC Neurol* 2015;15:220.
109. Sufaro Y, Avraham E, Alguyn F, et al. Unfavorable functional outcome is expected for elderly patients suffering from acute subdural hematoma even when presenting with preserved level of consciousness. *Journal of Clinical Neuroscience* 2019;67:167-171.
110. Van Essen TA, Dijkman MD, Cnossen MC, et al. Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma in an Aging Population. *Journal of Neurotrauma* 2019;36(7):1184-1191.
111. Park JK, Lee K, Bae KG, et al. Thin Acute Subdural Hematoma: Part 3 : Result of Conservative Treatment. *Journal of Korean Neurosurgical Society* 2021;19(7):937-944.
112. Mathew P, Oluoch-Olunya DL, Condon BR, et al. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993;121(3-4):100-108.
113. Wong. Criteria for conservative treatment of supratentorial acute subdural haematomas. *Acta Neurochir Wien* 2005;(135):38-43.
114. Sousa J, Sharma RR, Pawar SJ, et al. Long term outcome in patients with severe head injury and bilateral fixed dilated pupils. *Neurol India* 2002;50(4):430-435.
115. Ahmed E, Aurangzeb A, Khan SA, et al. Frequency of conservatively managed traumatic acute subdural haematoma changing into chronic subdural haematoma. *Journal of Ayub Medical College* 2012;24(1):71-74.
116. Izumihara A, Yamashita K, Murakami T. Acute subdural hematoma requiring surgery in the subacute or chronic stage. *Neurologia Medico-chirurgica* 2013;53(5):323-328.
117. Kim B-J, Park K-J, Park D-H, et al. Risk factors of delayed surgical evacuation for initially nonoperative acute subdural hematomas following mild head injury. *Acta Neurochir* 2014;156(8):1605-1613.
118. Laviv Y, Rappaport ZH. Risk factors for development of significant chronic subdural hematoma following conservative treatment of acute subdural hemorrhage. *Br J Neurosurg* 2014;28(6):733-738.
119. Bajsarowicz P, Prakash I, Lamoureux J, et al. Nonsurgical acute traumatic subdural hematoma: what is the risk? *Journal of Neurosurgery* 2015;123(5):1176-1183.
120. Zhuang Z, Luo J, Ou C, et al. The clinical and CT features of rapid spontaneous resolution of traumatic acute subdural hematoma: A retrospective study of 14 cases. *Brain Inj* 2015;29(10):1239-1245.
121 Son S, Yoo CJ, Lee SG, et al. Natural course of initially non-operated cases of acute subdural hematoma: the risk factors of hematoma progression. *Journal of Korean Neurosurgical Society* 2013;54(3):211-219; doi:10.3340/jkns.2013.54.3.211.
122. Van Essen TA, Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir* December 2018:1-15.

PART II

CURRENT PRACTICE

Chapter 4

Neurosurgical treatment variation of traumatic brain injury: evaluation of acute subdural hematoma management in Belgium and The Netherlands

Van Essen TA, de Ruiter GC, Kho KH, Peul WC.

J Neurotrauma. 2017 Feb 15;34(4):881-889.

Portions of this work were presented at the 11th Symposium of the International Neurotrauma Society, Budapest, Hungary, March 19-23, 2014.

ABSTRACT

Several recent global traumatic brain injury (TBI) initiatives rely on practice variation in diagnostic and treatment methods to answer effectiveness questions. One of these scientific dilemmas, the surgical management of the traumatic acute subdural hematoma (ASDH) might be variable between countries, between centers within countries and even between neurosurgeons within a center and hence amenable for a comparative effectiveness study. The aim of this questionnaire was to explore treatment variation for ASDH between neurosurgeons in similar centers in a densely populated geographical area. An online questionnaire, involving treatment decisions on 6 case vignettes of ASDH, was sent to 93 neurosurgeons in The Netherlands and Belgium. Clinical and radiological variables differed per case. Sixty neurosurgeons filled out the questionnaire (response rate 65%). For case vignettes with severe TBI and an ASDH there was a modest variation for the decision to evacuate the hematoma and a large variation for the decision to combine the evacuation with a decompressive craniectomy. The main reasons to operate were 'neurological condition' and 'mass effect'. For ASDH and mild/moderate TBI there was large variation for operating or not, whereas 'hematoma size' was the predominant motivation for surgery. Significant intercenter variation for the decision to evacuate the hematoma was observed ($p = 0.01$). Most pronounced was that one out of seven (14%) neurosurgeons in one region chose a surgical strategy compared to nine out of ten (90%) in another region for the same case. In conclusion, variation exists in the neurosurgical management of TBI within an otherwise homogeneous setting. This variation supports the methodology of the international CENTER-TBI initiative and shaped the Dutch Net-QuRe initiative.

Keywords:
Traumatic brain injury, acute subdural hematoma, treatment variation.

INTRODUCTION

Current and future research initiatives in traumatic train injury (TBI) aim to answer effectiveness questions using a comparative effectiveness approach.[1] While most traditional clinical trials have shown disappointing results due to methodological and ethical constraints,[2,3] this comparative effectiveness methodological strategy seems promising for TBI since considerable unexplained variation in outcome has been reported and hypothesized to be due to variation in standard practice care. To relate the practice variation to the outcome variation, however, several of the hypothesized assumptions, imposed by the ambition to do effectiveness research using observational data, have to be explored. Specifically, for many neurosurgical effectiveness questions, mainly regarding severe TBI patients and/or patients with CT abnormalities, practice variation in care has to be present and be quantifiable in the data while at the same time other factors (i.e. confounders) need to be uniformly distributed. Therefore, in preparation for the Dutch Neurotraumatology Quality Registry (Net-QuRe) and Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) of one of the important neurosurgical questions, we aimed to explore whether a detailed analysis would lead to a quantification of the hypothesized practice variation in an otherwise homogeneous area. The question entails the clinical dilemma 'to operate or not in acute subdural hematoma (ASDH)'.

When confronted with a patient with TBI and an accompanying ASDH neurosurgeons, are faced with several management dilemmas. The first and most challenging question is whether or not emergency surgery is indicated. The decision whether to evacuate an ASDH is based on a number of factors including the patient's age, Glasgow Coma Score (GCS), pupillary status, comorbidities, computed tomography (CT) findings and subsequent neurological deterioration or not.[4] Prompt surgical evacuation can successfully decrease mortality but it is also known that despite surgical and intensive care treatment many patients die or have an unfavorable functional outcome.[5-8] On the other hand, a substantial portion of patients managed conservatively may have long term favorable outcomes.[9-11]

The second question is whether evacuation of the hematoma should be accompanied by a bony decompression (a decompressive craniectomy, DC). This decision seems to be mainly influenced by the following factors: observation of brain swelling during the surgery, intuitively to be expected secondary brain swelling by the treating clinicians (neurosurgeon, neurologist or intensivist), medically intractable intracranial hypertension in the course of intensive care treatment, presence of penetrating (blast) brain injury or solely as the result of the hospital's protocol.[4,12,13] The known complications of decompressive surgery have to be balanced against the risk of uncontrolled brain swelling.[14,15]

Ethical considerations complicate these decisions even more. Treatment decisions do not merely depend on efficacy based on mortality and functional outcome, but should also consider patient autonomy and incorporate perceived cognitive and somatic disability. Evacuation of the hematoma can be lifesaving but at the same time may lead to survival of severely disabled patients with a poor quality of live or even absence of autonomous cognitive functioning and rational thinking.[16,17]

In addition, these complicated decisions often have to be made in far from ideal conditions, constrained by time, suffering from incomplete information of patients' medical history. And due to 24/7 occurrence, often ensue at difficult moments, in the middle of the night or weekend when regular consultation between senior staff-colleagues is difficult and important treatment choices frequently have to be made by one medical expert, mostly the neurosurgeon on call.

Society, and thereby future patients in particular, will have the opinion that these difficult decisions in TBI management follow protocolled schemes and algorithms, thereby excluding doubt. The contrary of this assumption might however be more true. The surgical decision-making is hampered by the lack of evidence-based selection criteria as a consequence of the absence of robust scientific grounds for surgical indications.[18] The most recent and most broadly known guidelines, The Brain Trauma Foundation (BTF) guidelines on the surgical management of ASDH[4] are deduced from studies with a maximum of - merely - level 3 evidence. Since then, the only study exceeding this level[19] has also not led to clearly defined surgical indications of procedures for patients with an ASDH. Generally, in TBI, there is a lack of high quality evidence relating surgery to outcome, mostly due to methodological constraints.[20,21]

Thus, confronted with a patient with a traumatic ASDH, clinicians have to deal with multiple clinical and radiological variables, in a very limited time frame and with a shortage of data or predictive outcomes. In this setting the training background of the trauma team, the culture of the way treatment is being performed in that particular hospital and the intuition of the neurosurgeon on call could be the most important factors that predict surgical decisions. How this echoes into current practice patterns with possibly variation in TBI management protocols has been scarcely investigated. Hypothetically, no large difference in background and university training of neurosurgeons exists in Belgium and The Netherlands and, therefore, a low practice variation is to be expected. So far, no study has evaluated if this varying trauma management could also be the result of a variable view among neurosurgeons.

Therefore, we performed an online questionnaire study with questions on the clinical management of hypothetical cases, based on real patients with an ASDH, to determine, whether variability in view exists among neurosurgeons on treatment of the ASDH and which potential factors might influence surgical decision-making

by presenting cases that varied for the patient's age, severity (in GCS), thickness of the hematoma and mass effect. The study was conducted in this area with the global goal to evaluate the differences in healthcare provider profile in a hypothetically homogeneous area.

METHODS

The Netherlands and Belgium are small countries with a high population density. Neurosurgical care for patients with TBI is provided at 11 level I trauma centers, serving separate areas according to regional referral policies. Acute trauma care is uniformly organized for all patients, with equal distribution of resources among hospitals. Almost all inhabitants (98%) are within 30 minutes reach from a trauma center (Fig. 1).

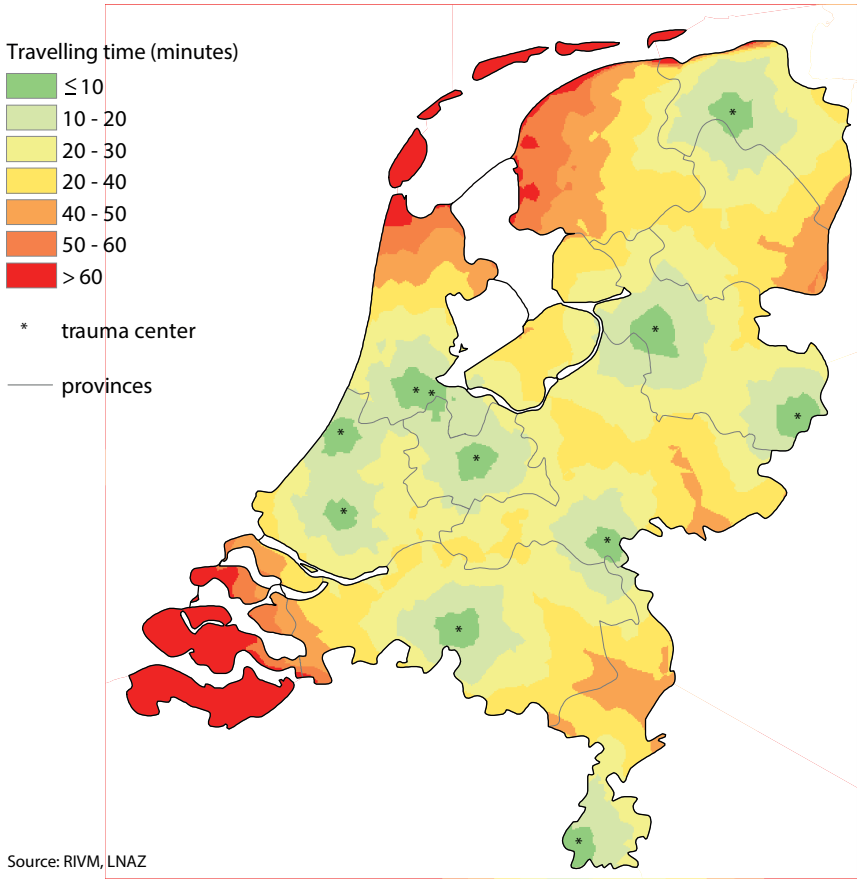


Figure 1. Average traveling time to a trauma center in the Netherlands 2011.

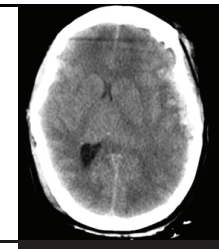
Regular day-to-day cases with TBI and CT brain abnormalities suspecting ASDH were selected. The medical history and CT scans of these patients with traumatic ASDH were retrieved from medical records of Leiden University Medical Center, Medical Center Haaglanden and University Hospitals Leuven. We reviewed these cases and selected 6 cases, based on individual variability between patients, with different medical history, based on severity, age, duration between the accident and presentation to the hospital (Fig. 2). In order to examine potential variation in treatment we selected 4 cases that evoked discussion a priori in the author group and 2 cases that did not (as a control group). Case 1, 2 (control) and 3 represent severe and moderate TBI, i.e. GCS 3-12, and cases 4, 5 (control) and 6 represent mild TBI, i.e. GCS 13-15. The cases were presented in a fixed random order (i.e. equal for every respondent). The provided information per case consisted of the clinical characteristics depicted in Figure 2 and three axial CT coupes (one of which is shown in the figure). In Table 2 the questions regarding these cases are listed.

Dutch and Belgian neurosurgical department chiefs were asked by email whether we could send a survey on operative management of the traumatic acute subdural hematoma to their staff members. An invitation for the online questionnaire was subsequently sent to the staff clinicians, fellows and chief residents working in the responding neurosurgical departments. The online survey was made and disseminated using the web survey tool SurveyMonkey (SurveyMonkey Inc., Palo Alto, California, USA, www.surveymonkey.com).

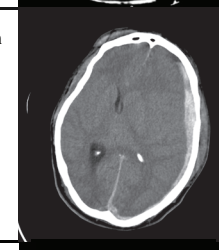
Collected variables of the neurosurgeon were the age, location of residency program, current clinical department and practicing time (time since finishing residency). The various treatment options were analyzed for each case in general (all neurosurgeons). Whether the responders would have operated or not was also analyzed per center (or geographical region) if more than half of the employed staff clinicians responded. The question whether to combine the evacuation with a decompressive procedure, was also regionally analyzed but only for the severe TBI cases (1,2, and 3).

Since the outline of this study was descriptive, only a few statistical analyses were employed. Statistical comparisons were limited to the analysis of regional variation using chi-square test and Fisher's exact test when appropriate. For statistical analysis SPSS 20.0 (IBM, Chicago, Il, USA) was used. P-values < 0.05 were considered to statistical significance. The missing values (not answered questions) for all questions were accepted up to 4% for all questions. Missing data were left out and observed data were analyzed unless stated otherwise.

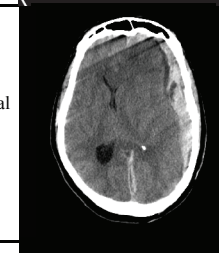
Case 1
Woman, 27 years, motor vehicle accident half hour ago, fall on right side of head.
History: blank. Medication: none.
Neurological exam
E3M5V1, localizes with right arm, not with left arm.
Cranial nerves: normal pupillary reactivity and corneal reflex on both sides.
CT
Left-sided ASDH, contusions left frontotemporal, impression fracture petrous bone right. Midline shift 1 cm to the right. Obliterated basal cisterns.



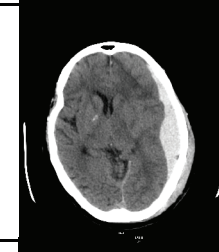
Case 2
Man, 28 years, assault 40 minutes ago, GCS of E1M2V2 and normal pupillary reactivity both sides.
History: unknown. Medication: unknown.
Neurological exam
E1M2V2, no lateralization. Cranial nerves: normal pupillary reactivity on both sides.
CT
Left-sided ASDH, severe midline shift to the right.



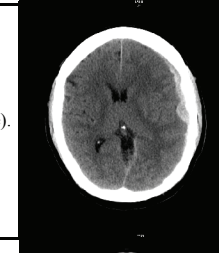
Case 3
Man, 72 years, found unconscious, unclear since when.
History: atrial fibrillation. Medication: acenocoumarol.
Neurological exam
E1M2V1. Cranial nerves: pupil anisocoria (left > right), left pupil nonreactive, normal corneal and oculocephalic reflexes.
Blood results
INR 3,6
CT
Large left -sided ASDH with severe midline shift.



Case 4
Man, 79 years, fall on head couple of hours ago. History: diabetes mellitus and hypertension.
Medication: no anticoagulants, no aspirin.
Neurological exam
E3M6V5. Cranial nerves: no abnormalities.
Motor function: paretic right arm (MRC 4), no other paresis.
CT
Left-sided ASDH of 20 mm. Midline shift 9 mm. Normal basal cisterns.



Case 5
Man, 43 years, assault 2 days ago, headache since then, today nausea and vomiting, no loss of consciousness.
History: aorta insufficiency grade 1 - 2, atrial fibrillation. Medication: acenocoumarol.
Neurological exam
EMV 15. No aphasia. Cranial nerves: normal. Motor function: slight drifting right arm (Barré).
Blood results
INR 2.36.
CT
Left-sided ASDH of 10 mm, midline shift of 5 mm.



Case 6
Woman, 79 years, motor vehicle accident, remembers everything, mild headache without other symptoms.
History: Percutaneous coronary intervention. Medication: aspirin.
Neurological exam
Wound on back of head.
EMV15. No abnormalities.
CT
Left-sided ASDH with mild midline shift to the right. Fracture line caudal side of maxillary sinus.

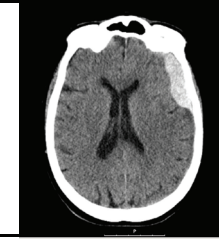


Figure 2. The six case vignettes and the accompanying CTs.

RESULTS

Neurosurgeon's characteristics

The survey was completed by 60 respondents (53 neurosurgeons and 7 chief residents) of a total of 93 invitations send out (response rate 65%). Of the respondents, 43 work in the Netherlands and 17 in Belgium. The responding neurosurgeons work in respectively Amsterdam, Enschede, Leiden/The Hague, Nijmegen, Rotterdam, Tilburg, Antwerp, Brussels or Leuven. Three clinicians did not report their center. The number of clinicians per center is kept anonymous. The respondents had a mean age of 44 years (range 30 – 67) with a median time since finishing residency of 12 years (Table 1).

Strategy towards patients with severe TBI and ASDH

For patients with severe TBI and ASDH (case 1, 2 and 3) there is variation in the decision to surgically evacuate the hematoma or not; respectively 88, 100 and 77 % answered 'yes' to the question 'would you operate or not?' and 23, 8.3 and 28% answered 'yes' to the question 'randomize or not?' (Table 2). The question 'DC or not?' resulted in respectively 74, 67 and 17% of 'yes' answers, indicating variation in type of surgery per case. In addition, respectively 5 (9.4%), 6 (10%) and 2 (4.3%) would choose to perform a DC intraoperatively only when the brain was considered to be swollen. For all other neurosurgeons a craniotomy was the preferred strategy. For the question 'ICP measurement?' respectively 72, 82 and 43% of neurosurgeons answered 'yes'. In case 1 all other neurosurgeons answered 'no' except for eight neurosurgeons (13%) that chose to place an ICP monitor depending on intraoperative brain swelling. In case 2 and 3 all other neurosurgeons did not choose to place an ICP sensor.

Table 1. Baseline characteristics

Responder's characteristics	Number of responders (%)
Number of responders	60 of 93 (65)
Male	55 (92)
Dutch	43 (72)
Age	44, range 30-67
Chief residents neurosurgery	7 (12)
Years since finishing residency	12, 14 IQR

IQR: interquartile range.

Table 2. Questions, possible answers and responses (proportions) with regard to the clinical case vignettes

		Answers (%)					
Questions	**Possible answers**	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
1. Would you perform an operation on this patient?	*Yes*	53 (88.3)	60 (100)	46 (76.7)	41 (68.3)	3 (5.0)	3 (5.0)
	No	7 (11.7)	0	14 (23.3)	19 (31.7)	57 (95)	57 (95)
2. Would you be willing to leave this decision (whether to operate or not) open for randomization in a study?	*Yes*	14 (23.3)	5 (8.3)	17 (28.3)	29 (48.3)	24 (40)	12 (20)
	No	45 (75) *	55 (91.7)	43 (71.7)	31 (51.7)	36 (60)	48 (80)
3. When answered 'yes' on Q1, what kind of operation would you perform?	*a) Craniotomy with evacuation of the hematoma*	5 (9.4)	14 (23.3)	35 (76.1)	39 (95.1)	2 (66.7)	2 (66.7)
	b) DC with evacuation of the hematoma	39 (73.5)	40 (66.7)	8 (17.4)	0	0	0
	c) Burr hole drainage	0	0	0	0	0	
	d) Another option, please specify: ... **	5 (9.4)	6 (10.0)	2 (4.3)	2 (4.9)	1 (33.3)	1 (33.3)
4. Would you place an ICP sensor?	*Yes*	43 (71.7)	49 (81.7)	26 (43.3)	3 (5.0)	0	0
	No	6 (10)	10 (16.7)	31 (51.7)	56 (93.3)	55 (91.7)	55 (91.7)
	Depends on intraoperative swelling	8 (13.3) *	0 *	0 *	0 *	0 *	0 *

* Numbers do not add up because some respondents did not answer.

** For case 1,2 and 3 the respondents answered that they would perform a decompressive craniectomy dependent on intraoperative swelling. For case 4, 5 and 6 the respondents would start dexamethasone and/or would perform a burrhole drainage in a later stage.

DC: decompressive craniectomy; ICP: intracranial pressure.

Strategy towards patients with mild TBI and ASDH

For the patients with mild TBI and ASDH (case 4, 5 and 6) there is considerable variation in the decision to surgically evacuate the hematoma or not (Table 2; 'operate or not?' respectively 68, 5.0 and 5.0% 'yes' answers; positive incentive for randomization respectively 48, 40 and 20%). DC was never chosen in mild cases. ICP measurement was chosen in three mild TBI cases (5.0% for case 4).

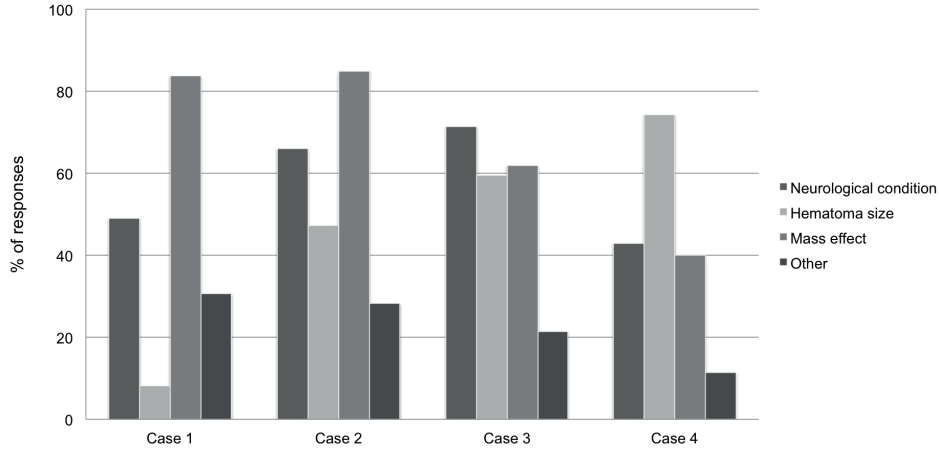


Figure 3. Graph illustrating the reason(s) for evacuation of the acute subdural hematoma, in percentages of responses (proportions).

The respondents had the choice to give multiple answers per case. Case 5 and 6 were not included since a minority of surgeons chose to operate (see Table 2). The numbered cases refer to the cases shown in figure 2.

Table 3. The relation between neurosurgeon's age and tendency to operate

Hypothetically operated (%)	Age		
	≤ 45 yrs	> 45 yrs	*p*
Case 1	31 (93.9)	18 (81.8)	0.20
Case 2	33 (100)	22 (100)	N/A
Case 3	23 (69.7)	18 (81.8)	0.31
Case 4	20 (60.6)	17 (77.3)	0.19
Case 5	2 (6.1)	1 (4.5)	1.0
Case 6	2 (6.1)	0 (0.0)	0.51
Total	111 (56.1)	76 (57.5)	0.80

Five respondents did not report their age. Yrs: years.

Table 4. The relation between region and tendency to operate

Hypothetically operated (%)	Regions					
	A (n = 3)	B (n = 7)	C (n = 16)	D (n = 10)	E (n = 7)	*p*
Case 1	2 (66.7)	6 (85.7)	14 (87.5)	10 (100)	85.7 (6)	0.49
Case 3	1 (33.3)	3 (42.9)	14 (87.5)	9 (90)	7 (100)	0.17
Case 4	0 (0)	1 (14.3)	13 (81.2)	9 (90)	6 (85.7)	0.01

Indications for surgery

For cases representing severe TBI the main reasons for surgery of the ASDH were 'neurological condition' and 'mass effect'. For the operated mild TBI case 'hematoma size' was the most important variable for the decision to operate (Fig. 3).

Age and practice variation

There was no association between age and tendency to operate for all six cases individual or overall (Table 3).

Regional variation

Region is associated with the decision to evacuate the hematoma or not (Table 4). For case 1, the proportion surgical strategies did not differ between regions. For case 3, neurosurgeons in region A and B were less aggressive, although not significantly, with regard to evacuating the hematoma compared to region C, D, and E. For case 4 there was a significant association between region and operating or not. Most notably, one out of seven (14%) of neurosurgeons in one region chose a surgical strategy compared to nine out of ten (90%) in another region for this case vignette. The intracenter variability, i.e. neurosurgeons within a center, is most pronounced for region B, as can also be deduced from Table 4. Lastly, there seems to be a moderate regional variation for the decision to combine the primary evacuation of the hematoma directly with a DC: in case one 57% of region B (n = 7) would perform a primary DC while 100 % of region C (n = 16).

DISCUSSION

Remarkably and in contrast to the author's hypothesis, this study suggests that standard treatment of (severe) TBI is highly variable due to a differing view on neurosurgical management despite the small countries, dense population and similar training curricula of trauma team physicians.

The survey results show that surgical decision making for patients with ASDH varies considerably in the Dutch speaking part of The Netherlands and Belgium. Practice variation in the treatment of ASDH between countries and within large countries like the USA is probable but was not suspected within small countries between hospitals or even between neurosurgeons. The variation in neurosurgical management between regions and between neurosurgeons is quite impressive and cannot be explained by the lack of evidence alone. Ethical considerations, personal opinions about value of a meaningful life from a humanistic perspective probably play an important role. It could be true that the reasons and predictions of clinicians in charge of TBI patients, driving life and death decisions, and, along

that line, how well a neurosurgeon or neurologist can actually predict the outcome, have a profound impact on the prognosis of TBI patients. Therefore, we feel that the different treatment strategies, reflected by the differing opinions in this study, should be related to the true outcome which can best be challenged by a comparative observational study of the different strategies with a comprehensive assessment of the long-term outcome (CENTER-TBI and Net-QuRe).

Specifically, this study shows that there seem to be two groups of TBI-ASDH patients that pose a challenging problem in surgical decision making, namely (1) patients with slight decrease in consciousness, i.e. mild TBI, combined with a large hematoma, and (2) elderly patients with a seemingly poor prognostic profile. These two groups will be discussed separately. A most remarkable finding was the regional variation (Table 4), which forms an important basis for future research on this subject and will be discussed subsequently.

Mild symptoms but large ASDH

The patients with slight decrease in consciousness and a large ASDH (thickness > 10 mm), such as case 4, appear to be a clinical challenge since there was a broad variation in operating or not as well as a high incentive to randomize. Presumably, neurosurgeons in favor of evacuation of the subdural hematoma estimate that a large ASDH leads to neurological deterioration or death by acting to slowly. Their suspicion is backed by the BTF guideline, which was devised in 2005 by an international panel of experts, that states that every ASDH with a thickness more than 10 mm and a midline shift over 5 mm should be evacuated as soon as possible, irrespective of neurological condition.[4] On the other hand, surgeons in favor of a conservative strategy do not want to expose the patient to the risks of a craniotomy without a more precise estimation of the chance of neurological deterioration when withholding an operation. It can be argued that the guideline and the evidence so far should not guide treatment since good quality comparative studies are lacking. Specifically, the reviewed studies of the BTF guideline were of a low level of evidence; retrospective, used small or selected study populations, and were performed more than 10 years ago. Since then, the only study exceeding this level is a Austrian prognostic study[19] Unfortunately, this study included patients with an ASDH due to severe TBI while patients with an ASDH due to mild or moderate TBI were not analyzed. This group represent up to 54% of patients with an ASDH.[9] Consequently, these results have not led to a clearly defined subset of surgical indications of procedures for patients with an ASDH.

Elderly with poor prognosis

The second category of ASDH patients that form a clinical dilemma is the prognostically unfavorable group of the elderly patient with severe TBI (as presented in case 3). Importantly, this clinical dilemma will only become more relevant since the number of elderly patients with a TBI is rapidly increasing[22] and specifically because subdural hematomas are more frequent in older patients.[23]

The treating neurosurgeon chooses not to operate because she/he believes the outcome will still be unfavorable with an operation. On the other hand, the reason to perform surgery could be that a neurosurgeon believes every patient deserves a chance to survive, how unlikely it may be. This tendency to act in severe TBI cases concerns especially young patients. In elderly patients some neurosurgeons are more reserved and abstain from cranial surgery as illustrated in case 3, probably due to an estimated poor prognosis.

To understand the variation in surgical decision-making is to understand the different metrics used to objectify outcome of patients. Clearly, the estimation of an unfavorable outcome or prognosis critically depends on how a worthwhile outcome is valued according to the treating neurosurgeon, trauma-surgeon, intensivist or neurologist. Although functional outcome scales are generally used to determine effectiveness in neurotraumatology studies (i.e. GOSE), neurosurgeons might consider other factors in the clinical setting. Often the conceptual issue quality of life (QoL) is routinely employed in clinical setting, especially in talking about the expected outcome of patients with a severe TBI. The neurosurgeon might estimate that the live that will be saved is not worth living or will result in a low quality of live, and therefore an evacuation is not performed.

In this context it is interesting to see how in a validated QoL instrument performs in ASDH patients. Therefore we performed a 4 year cohort study in Leiden and The Hague in which was shown that ASDH patients with a presenting GCS > 12 do not differ in their long term QoL (as measured by the Qolibri scale[24,25]) compared to surviving ASDH patients with a presenting GCS < 9.[26] This finding relates to the disability paradox where patients with severe disease or disability do not necessarily report a poor QoL.[27]

Surgical decision making in ASDH

Making decisions under uncertainty, especially when time constrained, as is the case for patients with traumatic ASDH, is susceptible for bias [28] and thereby can lead to practice variation. Analyzing the factors associated with this variation will let us understand how the decisions come about and can be improved. The challenges in understanding surgical decision making have been described for patients with spontaneous intracerebral haemorrhage.[29] Each of these issues more or less can also

hamper surgical decision-making in traumatic ASDH. Explicitly, in this investigation, evidence is found for region as an important aggregating factor for the variation in surgical care. The most likely explanation for this result is a differing practice culture between institutions and training background of neurosurgeons.
Also, we like to elaborate on a possible explanation for the discrepancy in the presented variation between severe and mild cases. There was a higher positive incentive for randomization in cases with mild symptomatology (4,5 and 6) than in severe cases (1,2 and 3), possibly reflecting more uncertainty with regard to mild/moderate TBI and ASDH. However, although the percentages 'yes' for surgery in cases 1, 2 and 3 were relatively high, it is important to realize that variation thus exists even for severe neurotrauma cases, in which the decision whether to operate or not often is a matter of life or death. An important explanation could be that neurosurgeons are more convinced of the merits of rapid surgical evacuation in severe cases. In part this might also be explained by a human instinct to act or do something in a patient with a life-threatening condition.

Regional variation in the literature

Although no similar survey has been conducted, other studies have shown that variability in treatment of TBI exists. Rayan et al. showed that in only 17% of a random sample of (brain) trauma patients care was delivered according to the BTF guidelines,[30] suggesting a variable approach. In addition, in an international survey it was shown that there was a difference in point of view among neurosurgeons with respect to combining the evacuation of an ASDH with a DC.[31] Furthermore, intercenter variation in TBI has been shown to exist for referral policy, admission organization, intensive care management (including ICP treatment).[32-38]
The intercenter or regional variation in surgical treatment of ASDH has not been shown in the literature. For other life-threatening or emergency disorders it has been investigated and confirmed for the ruptured abdominal aneurysm[39] and the spontaneous intracerebral haemorrhage.[40]

Strengths and limitations of the study

The main strength of our study is the standardized manner the questionnaire was submitted to medical professionals. Although the senior authors had a strong belief in homogeneous results across neurosurgeons and regions, the study subjects did choose quite differently for the same patient. In the aforementioned studies on current practices in TBI management, variation can be explained by other factors, e.g. by different institutional infrastructure or resources, by divergent patient preferences or by case-mix.

In addition, for the first time the pivotal clinical dilemma whether 'to operate or not' is addressed because case vignettes are presented across the whole spectrum of TBI (GCS 3 to 15). Other studies focus on how care is provided for certain patient subgroups, i.e. with large ASDHs and/or severe TBI. Hence, mainly approaches are evaluated that go into managing high ICP with DC.[31,41] Thus, our study provides insight into the more real-life situation where neurosurgeons are confronted by ASDH patients with heterogeneous clinical and radiological factors.

A very important but inevitable limitation of this study is the set-up as a survey wherein the actual real-life clinical setting is lacking. In the clinical setting the studied decisions often have to be made in far from ideal circumstances with potentially fatal consequences. In contrast, the decisions in this questionnaire are purely complicated by patient characteristics. Nonetheless, while it is acknowledged that this lack of real-life conditions could influence every respondent differently, the main conclusion on variation in ASDH management is most likely justified.

Future direction: comparative effectiveness research

An explanation for the apparent lack of high degree evidence on surgical management for TBI is the difficulty of performing randomized clinical trials. Generally in TBI research, the heterogeneous study population of TBI, i.e. the multitude of patient characteristics and treatment variables, together with small patient numbers make powering clinical trials problematic[21] and, therefore, require an extensive investment of time and money. Specifically for efficacy research of surgical strategies, randomizing surgical treatments for TBI is difficult to perform because of ethical concerns of withholding a potentially lifesaving procedure. In the presented study this is reflected in the low motivation to randomize severe TBI cases. And even if a trial succeeds it regularly has limited external validity since the treatment effect has been evaluated in certain subgroups, with management protocols that are sometimes difficult to replicate in the whole population. The randomized controlled trials on the surgical treatment of TBI, the Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury (DECRA) study[15] and the Surgical Trial in Traumatic Intracerebral Haemorrhage (STITCH-Trauma)[42] trial are examples illustrative of these methodological difficulties.

Due to these methodological challenges, the focus of much TBI research in the last decades has been on suggestions for optimizing RCT design and new study designs in TBI.[2,3] A promising approach could be the so-called comparative effectiveness research (CER). In this design, the heterogeneity and variability, which trouble RCT, are accepted and exploited to study effectiveness of treatments as they occur in real-life practice. This CER analysis of (surgical) treatment for TBI is currently one of the goals of a Dutch initiative called Net-QuRe and an international research initiative

called CENTER-TBI of which the authors are scientific participants (www.center-tbi.eu). The natural existing variation in management shown in this questionnaire provides a strong incentive for such a pragmatic observational study where the variation in surgical strategies is compared between regions and/or neurosurgeons. The rationale for this effort is further strengthened by the fact that the variability in the field of TBI management goes alongside unexplained variability in outcome. In a study by Lingsma and colleagues[43] more than threefold differences were found in the probability over and above chance effects to have an unfavorable outcome between the centers, which could not be explained by adjustments for the most important predictors of outcome in TBI (age, GCS motor score and pupil reactivity). Hence, relating this unexplained variation in outcome to the current practice variation is a promising methodological strategy in the challenging field of TBI research.[2,44]

There is a large variation in management approach for the traumatic ASDH in a medically uniformly trained European region, being The Netherlands and Belgium. Interestingly, there was a regional variation in a surgical versus conservative approach. Ultimately, this variation in management should be exploited in a comparative effectiveness study.

Acknowledgements

The authors wish to thank prof. dr. J. Van Loon and dr. B. Depreitere (neurosurgeons, Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium) for their involvement in case selection, all Dutch and Belgian neurosurgeons who participated in filling out the questionnaire and dr. C.L. Vleggeert-Lankamp (neurosurgeon, Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands) for critical appraisal of the first draft of our manuscript.

Author disclosure statement

All authors declare no conflicts of interest.

REFERENCES

1. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; 76, 67–80.
2. Maas AIR, Menon DK, Lingsma HF, et al. Re-Orientation of Clinical Research in Traumatic Brain Injury: Report of an International Workshop on Comparative Effectiveness Research. *Journal of Neurotrauma* 2012 29, 32–46.
3. Tosetti P, Hicks RR, Theriault E, et al. Toward an international initiative for traumatic brain injury research. *Journal of Neurotrauma* 2013 30, 1211–1222.
4. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006 58, S16–24– discussion Si–iv.
5. Tallon JM, Ackroyd-Stolarz S, Karim SA, Clarke DB. The epidemiology of surgically treated acute subdural and epidural hematomas in patients with head injuries: a population-based study. *Can J Surg* 2008 51, 339–345.
6. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012; 154, 1555–1561.
7. Nijboer JMM, Van der Naalt J, Ten Duis HJ. Patients beyond salvation? Various categories of trauma patients with a minimal Glasgow Coma Score. *Injury* 2010 41, 52–57.
8. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304, 1511–1518.
9. Dent DL, Croce MA, Menke PG, et al. Prognostic factors after acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1995 39, 36–42– discussion 42–3.
10. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993 121, 100–108.
11. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998; 44, 868–873.
12. Bell RS, Mossop CM, Dirks MS, et al. Early decompressive craniectomy for severe penetrating and closed head injury during wartime. *Neurosurgical FOCUS* 2010; 28, E1.
13. Guerra WK, Gaab MR, Dietz H, et al. Surgical decompression for traumatic brain swelling: indications and results. *Journal of Neurosurgery* 1999; 90, 187–196.
14. Yang XF, Wen L, Shen F, et al. Surgical complications secondary to decompressive craniectomy in patients with a head injury: a series of 108 consecutive cases. *Acta Neurochir* 2008 150, 1241–7– discussion 1248.
15. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. *N Engl J Med* 2011 364, 1493–1502.
16. Cooper PR, Rovit RL, Ransohoff J. Hemicraniectomy in the treatment of acute subdural hematoma: a re-appraisal. *Surg Neurol* 1976; 5, 25–28.
17. Honeybul S, Janzen C, Kruger K, Ho KM. Decompressive craniectomy for severe traumatic brain injury: is life worth living? *Journal of Neurosurgery* 2013; 119, 1566–1575.
18. Servadei F, Compagnone C, Sahuquillo J. The role of surgery in traumatic brain injury. *Curr Opin Crit Care* 2007 13, 163–168.
19. Leitgeb J, Mauritz W, Brazinova A, et al. Outcome after severe brain trauma due to acute subdural hematoma. *Journal of Neurosurgery* 2012; 117, 324–333.
20. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. *Journal of Neurotrauma* 2002. 19, 503–557.
21. Roozenbeek B, Lingsma HF, Maas AIR. New considerations in the design of clinical trials for traumatic brain injury. *Clinical Investigation* 2012; 2, 153–162.
22. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013; 9(4):231-6.
23. Stocchetti N, Paternò R, Citerio G, et al. Traumatic Brain Injury in an Aging Population. *Journal of Neurotrauma* 2012; 29, 1119–1125.
24. Von Steinbüchel N, Wilson L, Gibbons H, et al. Quality of Life after Brain Injury (QOLIBRI): Scale Development and Metric Properties. *Journal of Neurotrauma* 2010; 27, 1167–1185.
25. Von Steinbuechel N, Petersen C, Bullinger M. Assessment of health-related quality of life in persons after traumatic brain injury-

development of the Qolibri, a specific measure. *Acta Neurochir Suppl* 2005; 93, 43–49.
26. Van Essen TA, De Ruiter GCW, Peul WC. Factors of influence on surgical decision making and outcome in patients with acute subdural hematoma: a retrospective study of 109 patients with evaluation of quality of life. Paper presented at the 11th Symposium of the International Neurotrauma Society March 19–23, 2014 Budapest, Hungary. *Journal of Neurotrauma* 31:A–1–A–73, 2014.
27. Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol* 2005; 24, S57–62.
28. Kahneman D. Thinking, Fast and Slow. *Macmillan* 2011.
29. Kelly ML, Sulmasy DP, Weil RJ. Spontaneous intracerebral hemorrhage and the challenge of surgical decision making: a review. *Neurosurgical FOCUS* 2013 34, E1.
30. Rayan N, Barnes S, Fleming N, et al. Barriers to compliance with evidence-based care in trauma. *J Trauma Acute Care Surg* 72, 585–92– discussion 592–3.
31. Kolias, AG, Belli A, Li LM, et al. Primary decompressive craniectomy for acute subdural haematomas: results of an international survey. *Acta Neurochir* 2012 154, 1563–1565.
32. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. *Acta Neurochir* 1999; 141, 223–236.
33. Bulger EM, Nathens AB, Rivara FP, et al. Management of severe head injury: institutional variations in care and effect on outcome. *Crit Care Med* 2002.30, 1870–1876.
34. Clifton GL, Choi SC, Miller ER, et al. Intercenter variance in clinical trials of head trauma--experience of the National Acute Brain Injury Study: Hypothermia. *Journal of Neurosurgery* 2001; 95, 751–755.
35. Ghajar J, Hariri RJ, Narayan RK, et al. Survey of critical care management of comatose, head-injured patients in the United States. *Crit Care Med* 2005 23, 560–567.
36. Hukkelhoven CWPM, Steyerberg EW, Farace E, et al. Regional differences in patient characteristics, case management, and outcomes in traumatic brain injury: experience from the tirilazad trials. *Journal of Neurosurgery* 2002; 97, 549–557.
37. Jennett B, Teasdale G, Galbraith S, et al. Severe head injuries in three countries. *Journal of Neurology, Neurosurgery & Psychiatry* 1977 40, 291–298.
38. Stocchetti N, Penny K, Dearden M, et al. Intensive care management of head-injured patients in Europe: a survey from the European Brain Injury Consortium. *Intensive Care Medicine* 2001; 27, 400–406.
39. Brattheim BJ, Eikemo TA, Altreuther M, et al. Regional Disparities in Incidence, Handling and Outcomes of Patients with Symptomatic and Ruptured Abdominal Aortic Aneurysms in Norway. *European Journal of Vascular and Endovascular Surgery* 2012 44, 267–272.
40. Gregson BA, Mendelow AD. International Variations in Surgical Practice for Spontaneous Intracerebral Hemorrhage. *Stroke* 2003; 34, 2593–2597.
41. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–1192.
42. Mendelow AD, Gregson BA, Rowan EN, et al. Early Surgery versus Initial Conservative Treatment in Patients with Traumatic Intracerebral Hemorrhage (STITCH[Trauma]): The First Randomized Trial. *J Neurotrauma* 2015 Sep 1;32(17):1312-23.
43. Lingsma HF, Roozenbeek B, Li B, et al. Large Between-Center Differences in Outcome After Moderate and Severe Traumatic Brain Injury in the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) Study. *Neurosurgery* 2011; 68, 601–608.
44. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurgical FOCUS* 2012; 33, E3.

Chapter 5

Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study

Van Essen TA, den Boogert HF, Cnossen MC, de Ruiter GCW, Haitsma I, Polinder S, Steyerberg EW, Menon D, Maas AIR, Lingsma HF, Peul WC; CENTER-TBI Investigators and Participants.

Acta Neurochir (Wien). 2019 Mar;161(3):435-449.

Portions of this work were presented at the 13th Symposium of the International Neurotrauma Society, Toronto, Canada, August 11-16, 2018.

ABSTRACT

Background

Neurosurgical management of traumatic brain injury (TBI) is challenging, with only low-quality evidence. We aimed to explore differences in neurosurgical strategies for TBI across Europe.

Methods

A survey was sent to 68 centers participating in the Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. The questionnaire contained 21 questions, including the decision when to operate (or not) on traumatic acute subdural hematoma (ASDH) and intracerebral hematoma (ICH), and when to perform a decompressive craniectomy (DC) in raised intracranial pressure (ICP).

Results

The survey was completed by 68 centers (100%). On average, 10 neurosurgeons work in each trauma center. In all centers a neurosurgeon was available within 30 minutes. Forty percent of responders reported a thickness or volume threshold for evacuation of an ASDH. Most responders (78%) decide on a primary DC in evacuating an ASDH during the operation, when swelling is present. For ICH, 3% would perform an evacuation directly to prevent secondary deterioration and 66% only in case of clinical deterioration. Most respondents (91%) reported to consider a DC for refractory high ICP. The reported cut-off ICP for DC in refractory high ICP, however, differed: 60% uses 25 mmHg, 18 % 30 mmHg and 17 % 20 mmHg.
Treatment strategies varied substantially between regions, specifically for the threshold for ASDH surgery and DC for refractory raised ICP. Also, within center variation was present: 31% reported variation within the hospital for inserting an ICP monitor and 43% for evacuating mass lesions.

Conclusion

Despite a homogeneous organization, considerable practice variation exists of neurosurgical strategies for TBI in Europe. These results provide an incentive for comparative effectiveness research to determine elements of effective neurosurgical care.

INTRODUCTION

Neurosurgical decision-making in patients with traumatic brain injury (TBI) is often challenging for several reasons. First, no two TBI patients are identical – clinical and radiological findings may differ greatly.[1] Second, there is no high-quality evidence to support the range of possible neurosurgical procedures in TBI. Indications for surgical management are summarized in the Brain Trauma Foundation guidelines,[2] but are merely based on retrospective studies of small groups of selected patients. These guidelines provide general advice on surgical indications for evacuation of acute epidural (EDH), acute subdural (ASDH) and contusions/intracerebral hematomas (ICH) based on the size of the hematoma and midline shift. The guidance for decompressive surgery is even less clear. It is mostly performed to decrease raised intracranial pressure (ICP), either as a primary procedure in an acute setting, or as a secondary procedure to deal with diffuse edema or peri-contusional swelling. The guidelines state that this latter use of secondary decompression can reduce ICP, but does not necessarily improve outcome.[3] More fundamentally, the rationale for ICP monitoring has been challenged by the BEST-TRIP randomized controlled trial (RCT), which found no benefit of a management protocol based on intracranial pressure monitoring, compared to one based on serial imaging and clinical examination. These results have generated doubts regarding ICP monitoring.[4-8] Overall, there is no clear consensus on the indications, extent and timing of surgery.[9]

This limited high quality evidence for surgical management in TBI arises from a lack of RCTs, which may be difficult to conduct due to pragmatic, ethical and methodological barriers.[10] However, observational studies to determine effectiveness are more prone for bias.[11] A promising alternative approach could be comparative effectiveness research (CER).[12,13] In this design, the heterogeneity and variability, that trouble RCTs in TBI, are accepted and exploited to study effectiveness of treatments as they occur in real-life practice. The current Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study aims to use CER methodology to study treatment effectiveness of several neurosurgical interventions.[14]

The aim of this study was to explore differences in neurosurgical strategies for TBI across Europe to provide a context for CENTER-TBI, an up-to-date insight into European neurosurgical management of TBI, and to identify naturally occurring variation between trauma centers in order to identify substrates for neurosurgical research questions that might be answered using CER in the study.

MATERIALS AND METHODS

This study was conducted within the setting of the international observational study CENTER-TBI.[14] Between 2014 and 2015, all centers participating in the international multicenter observational study CENTER-TBI (www.center-tbi.eu) were asked to complete a questionnaire on neurosurgical management of TBI (Supplementary file 1).[15] The questionnaire was sent to 71 centers (Figure 1), of which 5 centers dropped out and 2 joined in, resulting in 68 eligible centers from Austria (n=2), Belgium (n=4), Bosnia Herzegovina (n=2), Denmark (n=2), Finland (n=2), France (n= 7), Germany (n=4), Hungary (n=3), Israel (n=2), Italy (n=10), Latvia (n=3), Lithuania (n=2), Norway (n=3), Romania (n=1), Serbia (n=1), Spain (n=4), Sweden (n=2), Switzerland (n=1), The Netherlands (n=6) and The United Kingdom (n=7).

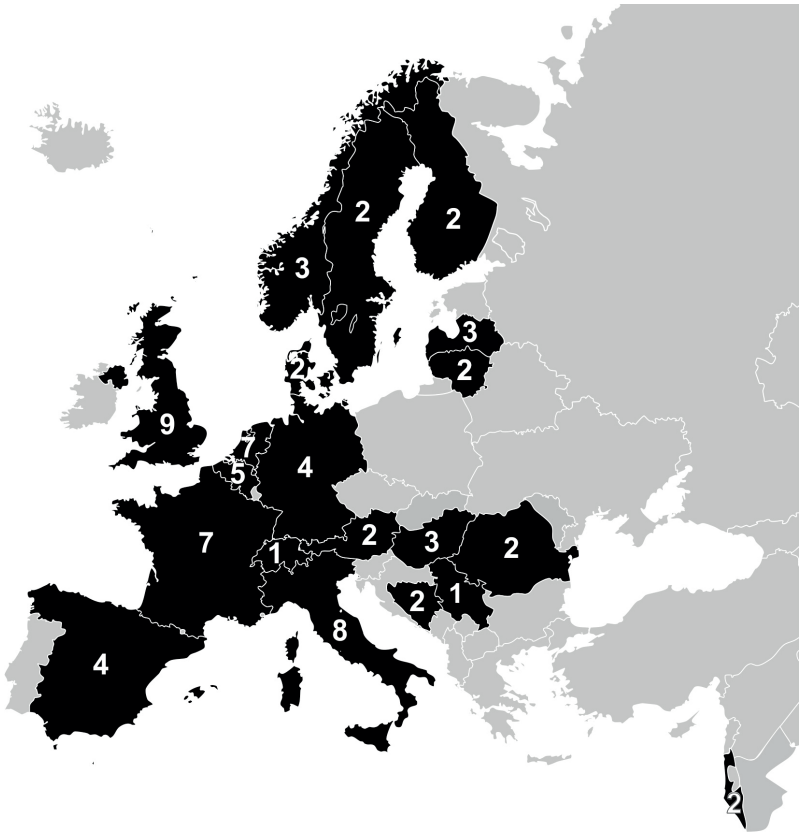


Figure 1. Centers and countries included in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study

Reprinted and updated from Cnossen et al. (2016) with permission from dr. Cnossen and Maas et al. (2015). Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury: a prospective longitudinal observational study. *Neurosurgery*, *76:67–80*, under a CC BY license, with permission from professor A.I. Maas

Questionnaire development and administration

We developed a set of questionnaires based on available literature and experts to measure the structure and processes of TBI care in individual centers. Details regarding this process and the questionnaires used are described in a separate paper.[15] Pilot testing was undertaken in 16 of the participating centers and feedback was incorporated into the final design.

One of the questionnaires was on neurosurgical standard practice. This survey contained 21 questions which could broadly be divided into 3 categories: 1) center characteristics and internal structure; 2) general (neuro)surgical trauma care and processes; 3) site specific neurosurgical management for treating ASDH, EDH, ICH, the use of DC, and policy with regard to orthopedic injuries in the context of patients who had suffered a TBI.

Questions either sought quantitative estimates of key metrics (e.g. annual surgical volume, staff size, ASDH thickness or ICP thresholds for surgery) or attempted to elicit the 'general policy' of the center. To capture the latter these questions were formulated in two ways: respondents were asked to estimate what the management strategy is in more than three quarters of patients in their center in a given context; or respondents were asked to indicate how often they used a particular surgical technique or how often specific factors influence their decision-making (never = 0 -10%, rarely = 10-30%, sometimes = 30-70%, frequently = 70-90 % and always 90-100%). The options 'frequently' and 'always' were interpreted as 'general policy', in line with a previous report[16] and similar to previous publications on other questionnaires.[15,17]

The reliability of the surveys were tested by calculation of concordance in a previous publication.[15] Overall, the median concordance rates between duplicate questions, was 0.81 (range 0.44 – 0.97) and specifically for the 'Neurosurgery' survey 0.78 (range 0.68 – 0.86).

Analyses

The median and interquartile range (IQR) were calculated for continuous variables, and frequencies were reported along with percentages for categorical variables. Countries were divided into seven geographic regions: Northern Europe (Norway 3, Sweden 2, Finland 2 and Denmark 2 centers), Western Europe (Austria 2, Belgium 4, France 7, Germany 4, Switzerland 1 and The Netherlands 6 centers), The United Kingdom (7 centers), Southern Europe (Italy 10 and Spain 4 centers), Eastern Europe (Hungary 3, Romania 1, Serbia 1 and Bosnia Herzegovina 2 centers), Baltic States (Latvia 3 and Lithuania 2 centers) and Israel (2 centers).

For the following neurosurgical treatment strategies we quantified regional differences: an absolute cutoff of hematoma thickness as an indication for surgery

for ASDH, DC in the primary evacuation of an ASDH, early/pre-emptive surgical evacuation for ICH, and DC as a general policy in case of refractory raised ICP.
To assess the association of region with one of these treatment choices, a logistic regression was performed with treatment choice (general policy or 'yes/no') as a dependent variable and the region (categorical) as independent variable. Nagelkerke R2 indicated the variance explained by geographic region. Analyses were done in IBM SPSS Statistics version 20 (IBM, Chicago, Il, USA).

RESULTS

Center characteristics

All 68 eligible centers completed the questionnaire on neurosurgery (response rate 100%). Questionnaires were mainly completed by neurosurgeons (n = 53, 78%), followed by local CENTER-TBI investigators (mainly research physicians or nurses: 19%). On average, 10 neurosurgeons (IQR 8-13) and 4 trauma surgeons (IQR 0-12) worked in each center. All centers reported that neurosurgical coverage was available 24 hours a day/7 days a week, either by way of in-house availability of a qualified neurosurgeon (47%), or the availability of such an individual in less than 30 minutes (53%) (Table 1).

General (neuro)surgical care and processes

Treatment decisions regarding cranial surgical interventions in TBI patients within the critical care ER and ICU period are in most centers determined by the neurosurgeon (n= 65, 96%), followed by the orthopedic surgeons and neuro-intensivist in respectively 3% (n=2) and 1% (n=1). Urgent neurosurgical interventions (ICP monitor device insertion not included) for life-threatening traumatic intracranial lesions, are made by the neurosurgeon in 98.5% and trauma surgeons in 1.5% of the centers. Raised ICP will almost always be incorporated in decision making, the time of day almost never (Figure 2).
With regard to extremities fractures, the general policy in 59 (87%) centers was so-called damage control with priority for TBI and delayed definitive treatment of the limb fractures (Table 2). This policy is protocolized in 21 centers (22%).
Of all centers, 58 (85%) estimated the space-occupying effect of traumatic lesions on the surrounding tissue by calculation of the thickness of the hematoma and midline shift on CT. A quarter of centers used actual volume measurement to make surgical decisions (Table 2).

Table 1. Characteristics of centers participating in neurosurgery survey

Characteristic	N completed	No. (%) or median (IQR)
Profession of respondent	68	
Neurologist		3 (4)
Neurosurgeon		53 (78)
Trauma surgeon		3 (4)
ED physician		1 (2)
Intensivist		1 (1)*
Administrative staff member		11 (16)*
CENTER-TBI local investigator		13 (19)*
Volume of surgeries in 2013[a]		
ASDH	59	25 (15-49)
ICH/contusion	58	10 (5-21)
EDH	59	10 (5-19)
DC		
Hemicraniectomy	57	10 (5-16)
Bifrontal	57	0 (0-2)
Removal bone flap	55	1 (0-3)
Ventriculostomy	57	7 (2-21)
Cranioplasty	56	10 (6-14)
Depressed skull fracture	57	5 (2-12)
Staffing (FTE)		
Neurosurgeons	66	10 (8-13)
Residents in training	65	5 (3-8)
Residents not in training	61	0 (0-3)
Trauma surgeons	64	4 (0-12)
Organization of care		
Neurosurgical decision making in ICU	68	65 (96)
Neurosurgeon		1 (3)
Trauma surgeon		0
Neurologist		1 (2)
Neurointensivist or general intensivist		
24/7 neurosurgical coverage**	68	32 (47)
Qualified neurosurgeon in-house		30 (44)
Resident neurosurgery in-house		36 (53)
Neurosurgeon within 30 minutes		11 (16)
Neurosurgical resident within 30 minutes		0 (0)
Neurosurgeon more than 30 minutes		

ASDH: acute subdural hematoma, EDH: epidural hematoma, ICH: intracerebral hematoma, DC: decompressive craniectomy, FTE: full time equivalent, ICU: intensive care unit

* Numbers do not add up because the local investigators also depicted their profession and one responder declared to be an intensivist as well as an administrative staff member.

** Multiple options possible

[a] Head trauma related surgeries

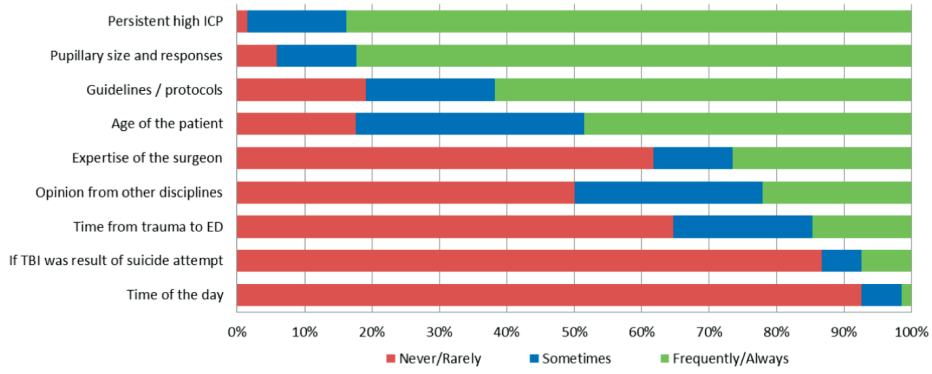


Figure 2. Factors of influence on neurosurgical decision making

Shown are the percentages of centers that would be never/rarely, sometimes or frequently/always influenced by the described factors in the decision to perform neurosurgical procedures. Question was completed by all 68 centers.

ICP: intracranial pressure; ED: Emergency Department

Neurosurgical management of ASDH, EDH, ICH, and the use of decompressive craniectomy

ASDH provided the highest volume of neurosurgical TBI cases, on average 25 cases per year. When performing a DC (for any indication), hemicraniectomy was the preferential technique, and bifrontal craniectomy was rarely performed (Table 1). Less than half of the centers (n=27, 40%) reported an absolute threshold for evacuating an ASDH. Four out of ten centers generally incorporate age in their decision for evacuating an ASDH (Table 2 and Figure 2).

ICH were seldom operated upon pre-emptively, but 67% of centers reported undertaking delayed surgery in the event of deterioration. Almost a third of centers reported within-center variations between individual neurosurgeons in decisions regarding surgical evacuation of contusions or traumatic ICH.

Only a very low proportion of centers would routinely perform a DC at the time of evacuation of either ASDH or ICH (respectively 6% and 1.5% of the centers). For refractory raised ICP, most centers (n= 64, 91%) would consider a decompressive craniectomy, while 32 (47%) see this as a general policy in their center (Figure 3, Table 2 and Figure in supplementary file 2). Ninety-six percent (n=65) reported to have a specific threshold for DC in refractory raised ICP. This was most commonly specified as 25 mmHg (n=39, 58%), followed by 30 mmHg (n=12, 18%) and 20 mmHg (n=11, 17%).

Table 2. Neurosurgical treatment policy of traumatic brain injury

Characteristic	N completed	No. (%) or mean (sd)
Structural estimation of mass lesions on CT*	68	
Visual intuition (e.g. no actual measurement)		27 (40)
Width, diameter and/or amount of MLS of the mass lesion		58 (85)
Volume measurements with imaging software		11 (16)
Volume measurements with direct calculation		17 (25)
Other		1 (2)
ASDH operation determinants		
Age considered important in surgery decision [A]	68	
Size (volume or thickness) threshold for surgery	68	26 (42)
Minimum volume or thickness:	28**	27 (40)
15 mm		
10 mm		2 (3)
10 mm and/or > 5 mm MLS		16 (24)
5 mm		2 (3)
ASDH thickness > width of cranium		3 (4)
Midline shift > thickness ASDH		3 (4)
DC indications	68	2 (3)
Routine		4 (6)
Intra-operative brain swelling		59 (86)
Sometimes as a second procedure in case of uncontrollable ICP		5 (7)
Never		0 (0)
ICH/contusion operation determinants		
General policy	68	
Pre-emptive (to prevent deterioration)		2 (3)
Delayed (after deterioration)		45 (66)
Variable (depends on surgeon)		18 (27)
Other		3 (4)
DC indications	68	
Routine		1 (2)
Intra-operative brain swelling		55 (81)
Sometimes as a delayed procedure in case of uncontrollable ICP		10 (15)
Never		2 (3)
Raised ICP determinants		
DC employed >70 % of refractory high ICP cases	68	32 (46)
Mostly early DC (within 6-12 hrs of refractory ICP)	64	32 (47)
Mostly late DC (as last resort to control ICP)	64	32 (47)
ICP threshold for DC	68	65 (96)
Raised ICP threshold for DC (mmHg):	64***	
30		12 (18)
25		39 (60)
20		11 (17)
15		1 (2)
Not standardized		1 (2)

Table 2. Neurosurgical treatment policy of traumatic brain injury (*continued*)

Characteristic	N completed	No. (%) or mean (sd)
DC indications considered*		7 (10)
Pre-emptive in raised ICP (not last resort)	68	64 (91)
Refractory raised ICP (last resort)		9 (13)
CT evidence of raised ICP		45 (66)
Intra-operative brain swelling		2 (3)
Routine with every ASDH or ICH evacuation		
Policy towards extremity limb fractures[B]		59 (87)
Damage control	68	9 (13)
Definitive care		

MLS: midline shift, BTF: Brain Trauma Foundation, ICP: intracranial pressure, hrs: hours

* Multiple options possible. ** One responder did not report a threshold for surgery while answering a specific threshold (10 mm). *** One responder reported to employ a threshold for DC in raised ICP while not giving their specific threshold. [A] The question was whether the responder considers if the decision on surgery in acute SDH is influenced by age (based on a general consensus in their respective center). [B] Damage control is focused on the TBI. All extremity fractures are stabilized, but definitive treatment delayed. Definitive care: the extremity fractures are operated as soon as possible.

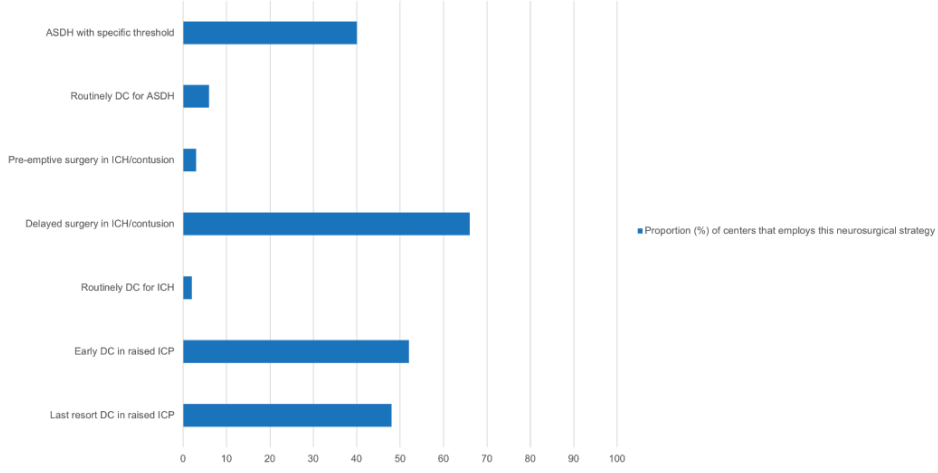


Figure 3. Treatment indications for neurosurgical interventions

Shown are the proportions of centers that generally have these specific preferences with regard to operating or not in ASDH, ICH and raised intracranial pressure respectively.

ASDH: acute subdural hematoma; DC: decompressive craniectomy; ICH: intracerebral hematoma; ICP: intracranial pressure

Guidelines and practice variation

Overall, the reported adherence to the BTF guidelines was high (Figure 4). The use of surgical interventions and specific indications for these interventions varied substantially within and between regions (Table 3). Surgical evacuation of ICH was

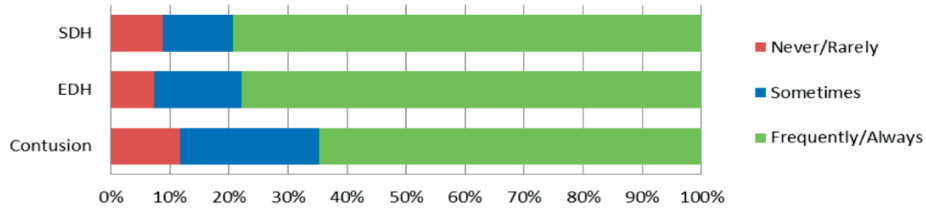


Figure 4. Brain Trauma Foundation guideline adherence

Shown are the percentages of centers that reported to never/rarely, sometimes or frequently/always follow the Brain Trauma Foundation guidelines for the management of SDH, EDH or contusions. Question was completed by 68 of the 68 centers.

TBI: traumatic brain injury; SDH: subdural hematoma; EDH: epidural hematoma

Table 3. Within- and between-region variation in surgical management

Decision	Northern Europe	Western Europe	United Kingdom	Southern Europe	Eastern Europe	Baltic States	Israel	Nagelkerke R^2 Value
ASDH								
- Size threshold for evacuation	56	29	0	29	71	80	100	0.34
- Routine or intraoperative DC	89	92	100	100	86	80	100	0.17
ICH/contusion								
- Pre-emptive surgery	0	0	0	7	0	20	0	0.35
Refractory raised ICP								
- DC	44	37	29	57	43	80	100	0.15

ASDH: acute subdural hematoma, ICH: intracerebral hematoma, DC: decompressive craniectomy, ICP: intracranial pressure

Table presents the proportion (%) of respondent within each region that indicated that they used the described strategy as their general policy for patients with respectively ASDH, ICH or refractory raised ICP. The Nagelkerke R^2 value represents the variation in treatment that can be explained by the region.

only performed in the Baltic States and Southern Europe and geographic region explained 35% of the variance in use of the intervention. Having a specific threshold for ASDH surgery and employing a DC for refractory raised ICP showed the largest within-region and also between-region variation. Lastly, when directly asked whether variation in specific management strategies exist, respectively 31% and 43% indicated to have a structural variation within their center staff with regard to ICP sensor insertion and mass lesion evacuation (Table 4).

Table 4. Neurosurgical decision making

Characteristic	N completed	No (%)
Structural variation* ICP monitor insertion	68	
No		47 (69)
Yes		21 (31)
Structural variation* mass lesion evacuation	65	
No		29 (43)
Yes		29 (43)
Depending on lesion type		7 (10)

ED: emergency department, GCS: Glasgow Coma Scale

* Structural variation refers to a situation in which one or more of the clinicians are generally more likely to perform the (diagnostic) intervention than others.

DISCUSSION

The aim of this study was to explore differences in neurosurgical strategies for TBI across Europe. We found substantial variability in practice and thereby provide useful indications regarding potential substrates for CER in CENTER-TBI. The structures and processes of neurosurgical care are generally homogeneous across centers with a comparable number of neurosurgeons, similar organization of neurosurgical coverage and uniform organization of responsibility for most surgical decisions on the ER and ICU. The indications for surgery, however, differ substantially with high within-region and between-region practice variations.

Contemporary neurosurgical care

There are no recent comparable studies providing an overview of neurosurgical management on this scale. Two recent national surveys, in The United Kingdom and the Republic of Ireland and The Netherlands, have shown a comparable variability among neurosurgeons regarding the decision to evacuate an ASDH or to perform a primary DC.[18,19]

When comparing our results to existing -much older- surveys, evacuation of a traumatic ICH seems to be less often considered than in the past.[20,21] Our results are concordant with older surveys in reporting variable use of DC for refractory raised ICP, despite the DECRA trial (the RECUEicp was not published yet).[22,23] Interestingly, although the mostly applied cutoff for DC in refractory is reported to be 25 mmHg (60%), a lower value, 20 mmHg, and a higher value, 30 mmHg, are both reported to be used in almost 20 % of centers.

More broadly, our results replicate past data that suggest poor guideline adherence and practice variability. Rayan et al. showed that in only 17% of a random sample of (brain) trauma patients care was delivered according to the BTF guidelines.[24] Of

note, in the current study, surveys were sent to the centers between 2014 and 2015, so the more recent, updated BTF guidelines were not published yet, although the update was for medical management mainly (except DC in refractory IC).[3]
Comparable questionnaires on other aspects of TBI care have recently been published for ER and ICU management that, without exception, show practice variation.[15,17,25,26] Practice variation has also been reported for other life-threatening or emergency disorders including ruptured abdominal aneurysm[27] and the spontaneous intracerebral hemorrhage.[28]

Strengths and limitations

A strength of the current study is the methodology that we used to investigate practice variation. First, detailed questions were posed to shed light on specific clinical decisions with regard to neurosurgical interventions. Subsequently, (objective) answers on amounts (volume load, mostly from in-hospital registries) were combined with qualitative information (estimations of general policies, using two approaches). When integrated with the high response rate and low amount of missing data in 68 centers, this overview provides a complete picture of reported neurosurgical care across Europe.
This study also had weaknesses. First, responses to the questionnaire may have been biased by the abstract nature of the questions posed, which neglected to provide a more concrete clinical context for judgments about reported practice. Although the respondents were experienced neurosurgeons with a scientific background, the difficulty of weighing individual patient characteristics with potentially fatal consequences can never be fully captured by a theoretical survey. In particular, the rational decision making can obviously be completely different due to the cognitive biases of neurosurgeons in the acute critical care period.
Second, there might be a concern as to how well the individual neurosurgeon respondent can represent the general center neurosurgical policy. Although we urged the respondent to report the general consensus on treatment at their center rather than individual management preferences (see Supplementary file 1), neurosurgical strategies may still be variable within centers between neurosurgeons. However, we did capture a qualitative assessment of this intra-center variability (Table 4). Third, we did not fully account for inherent regional variations such as evidence knowledge, caseload and case-mix due to referral patterns or admission policies, as a potential explanation for differences in neurosurgery policies. Variations in evidence knowledge for some questions, such as those on guidelines, are important. Moreover, while we did asses the center's caseload and case-mix, the caseload and case-mix of the (individual) respondent was not specifically asked. Fourth, the questions dealt with individual decisions in isolation, rather than the more complex

real-life situation where several competing priorities need to be addressed. Fifth, the reports may have been biased (in varying extents) towards how centers would have been liked to be perceived, rather than a faithful report of actual clinical policy and practice. This issue will be addressed by a planned comparison of these Provider Profiling responses with actual treatment strategies employed in patient-level data from these centers in the CENTER-TBI Core study.

Finally, our study sample represents centers participating in TBI-research which are likely specialized neurotrauma centers with a tendency to have practice that is skewed towards up-to-date knowledge. An example is the fact that almost half of all centers stated to have a neurosurgeon in house 24 hours a day. When studying all centers in Europe providing care to TBI patients, variability might be even larger.

Implications

Our results should be interpreted in combination with the current evidence on the effectiveness of different surgical strategies. For the use of DC in refractory raised ICP due to diffuse swelling, two RCTs have provided useful guidance. The DECRA trial showed that early use of DC for modest rises in ICP was associated with worse outcomes.[22] More recently however, after the conduct of this survey, the RESCUEicp trial showed that, when used for refractory severe intracranial hypertension, DC can save lives, but results in an excess of severely disabled survivors.[23] It is clear that the intervention is not uniformly beneficial: while some functional improvements occur by 12 months, many survivors remain severely disabled. Rescue-ICP was not published yet at the conduct of this study. In our study the majority of centers indicated that DC is often employed for both indications (pre-emptive and last resort). With regard to focal lesions, a recent study suggested that in patients with an ASDH an aggressive approach towards evacuation is associated with better outcome compared to a conservative approach.[29] Similar trends were noted in the STITCH-trauma trial, which suggested better outcome with early surgical management of ICH.[30] In our study, a minority of centers considers an early strategy for ICH evacuation.

Lastly, DC in the primary evacuation of an ASDH seems to be associated with more favorable outcomes.[31] There is no class 1 evidence, although the research question is currently being challenged in an RCT (Rescue-ASDH; ISRCT87370545). In the current survey standard (in some cases preventive) DC in ASDH evacuation is rarely employed but mostly done in case of intraoperative swelling.

There may be several explanations for the practice variation that we observed. Although high practice variation rates can be a sign of poor implementation of evidence based care, in this context it probably reflects the lack of strong evidence to underpin practice. In such a low evidence context, clinical decisions are not driven by careful consideration or penetration of the evidence, but by local customs and surgical

training, handed down over the years from one surgeon to the other in a given center (or country). The professional cultural drivers that underpin such learned treatment preferences are resistant to change, and provide an important hurdle to the design and conduct of randomized studies for neurosurgical interventions in TBI.[32]

Additionally, even where the results of RCTs are available, it is possible that many neurosurgeons do not think the RCT results applicable to their (individual) patients, or restrict their focus to short term clinical outcomes such as mortality and complication rates (instead of long term clinical or patient reported outcomes).[33]

The results of the questionnaire point out burning clinical questions for neurosurgery in TBI. For ASDH and ICH, important questions include whether to operate or not, the timing of operative evacuation, and whether or not a primary DC should be undertaken. Future studies should address these questions. For DC, the variation should lead to studies exploring the lack of evidence penetration, in addition to studying effectiveness of DC in refractory raised ICP.

While RCTs may provide the security of randomisation as a basis for examining answering these questions, RCTs have no successful history in TBI due to various reasons.[12] The CENTER-TBI Provider Profiling exercise has revealed large practice variation that can be related to variation in patient outcome.[34] Such a CER approach may be a pragmatic alternative to RCTs.

Therefore, different steps are required. Firstly, to specify, ideally a-priori, how and where treatment variation occurs. This was one of the goals of this provider profiling. Secondly, the CENTER-TBI Core Study will need to collect patient-level data from a large variety of centers, capturing the range of treatment variation and relate it to outcome. The main challenge is to disentangle the effect of specific surgical strategies in a center from other regional care variation that might affect outcome. To do so we propose random-effect models in which the effect of 'surgical strategy' on outcome is estimated with adjustment for other between-hospital differences in a random effect for hospital.[19,29,35]

Conclusions

This survey study explored differences in neurosurgical strategies for TBI. Current neurosurgical care differs within Europe (and Israel), while the organization of trauma centers does not. This variation in practice likely reflects the lack of high-quality evidence for these important, potentially life-saving, emergency neurosurgical interventions. In addition, local professional culture may drive practice in ways that are not dependent on the availability or penetration of evidence. The resulting entrenched practice variation does not facilitate equipoise that makes RCTs easy to deliver. CER may provide a pragmatic approach to generate evidence on optimal neurosurgical strategies for TBI patients.

Compliance with ethical standards

This study was funded by The European Union seventh Framework Program (grant 602150) for Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) and the 'Hersenstichting Nederland' (Dutch Brain Foundation, grant PS2014-06) for The Dutch Neurotraumatology Quality Registry (Net-QuRe).

Author TvE declares that he has no conflict of interest. Author HdB declares that he has no conflict of interest. Author MC declares that she has no conflict of interest. Author GdR declares that he has no conflict of interest. Author IH declares that he has no conflict of interest. Author SP declares that she has no conflict of interest. Author ES declares that he has no conflict of interest. Author DM declares that he has no conflict of interest. Author AM declares that he has no conflict of interest. Author HL declares that she has no conflict of interest. Author WP declares that he has no conflict of interest.

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

The CENTER-TBI Investigators and Participants and their affiliations are listed in the Appendix (available online):

https://link.springer.com/article/10.1007/s00701-018-3761-z#appendices

Further electronic supplementary material:

https://link.springer.com/article/10.1007/s00701-018-3761-z#Sec15

Supplemental material 1. Questionnaire neurosurgery.

Supplemental material 2. Supplementary figure, The use of a decompressive craniectomy.

REFERENCES

1. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology* 2008;7(8):728–41.
2. Bullock MR, Chesnut R, Ghajar J, et al. Introduction. *Neurosurgery* 2006;58(Supplement):S2–1–S2–3.
3. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2016; 1.
4. Albuquerque FC. Intracranial pressure monitoring after blunt head injuries: conflicting opinions. *World Neurosurg* 2013;79(5-6):598.
5. Chesnut RM, Temkin N, Carney N, et al. A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury. *N Engl J Med* 2012; 367(26):2471–81.
6. Ghajar J, Carney N. Intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2013; 368(18):1749.
7. Kahle KT, Duhaime A-C. Intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2013; 368(18):1750.
8. Mattei TA. Intracranial pressure monitoring in severe traumatic brain injury: who is still bold enough to keep sinning against the level I evidence? *World Neurosurg* 2013; 79(5-6):602–4.
9. Servadei F, Compagnone C, Sahuquillo J. The role of surgery in traumatic brain injury. *Curr Opin Crit Care* 2007; 13(2):163–8.
10. Bragge P, Synnot A, Maas AI, et al. A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury. *Journal of Neurotrauma* 2016; 33(16):1461–78.
11. Bosco JLF, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *Journal of Clinical Epidemiology* 2010; 63(1):64–74.
12. Maas AIR, Menon DK, Lingsma HF, et al. Re-Orientation of Clinical Research in Traumatic Brain Injury: Report of an International Workshop on Comparative Effectiveness Research. *Journal of Neurotrauma* 2012; 29(1):32–46.
13. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurgical FOCUS* 2012;33(1):E3.
14. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76(1):67–80.
15. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLoS ONE* 2016;11(8):e0161367.
16. Hesdorffer DC, Ghajar J. Marked Improvement in Adherence to Traumatic Brain Injury Guidelines in United States Trauma Centers. *The Journal of Trauma: Injury, Infection, and Critical Care* 2007;63(4):841–8.
17. Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Critical Care* 2017;21(1):233.
18. Kolias AG, Scotton WJ, Belli A, et al. Surgical management of acute subdural haematomas: current practice patterns in the United Kingdom and the Republic of Ireland. *Br J Neurosurg* 2013;27(3):330–3.
19. Van Essen TA, De Ruiter GCW, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *Journal of Neurotrauma* 2017 Feb 15;34(4):881-889.
20. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–92.
21. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. *Acta Neurochir* 1999;141(3):223–36.
22. Cooper DJ, Nichol A, Hodgson C. Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med* 2016;375(24):2402.
23. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med* 2016;375(12):1119–30.
24. Rayan N, Barnes S, Fleming N, et al. Barriers to compliance with evidence-based care in trauma. *J Trauma Acute Care Surg* 2012;72(3):585–92–discussion592–3.
25. Foks KA, Cnossen MC, Dippel DWJ, et al. Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: A survey of 71 neurotrauma centers participating in the

CENTER-TBI study. *Journal of Neurotrauma* 2017; Sep 1;34(17):2529-2535
26. Huijben JA, van der Jagt M, Cnossen MC, et al. Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Journal of Neurotrauma* 2017; neu.2017.5194.
27. Brattheim BJ, Eikemo TA, Altreuther M, et al. Regional Disparities in Incidence, Handling and Outcomes of Patients with Symptomatic and Ruptured Abdominal Aortic Aneurysms in Norway. *European Journal of Vascular and Endovascular Surgery 2012*; 44(3):267–72.
28. Gregson BA, Mendelow AD. International Variations in Surgical Practice for Spontaneous Intracerebral Hemorrhage. *Stroke* 2003;34(11):2593–7.
29. Van Essen TA, Dijkman M, Cnossen MC, et al. Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population. *Journal of Neurotrauma* 2019; Apr 1;36(7):1184-1191.
30. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with traumatic intracerebral haemorrhage [STITCH(Trauma)]: the first randomised trial. *Journal of Neurotrauma* 2015; 32(17):1312-23.
31. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012; 154(9):1555–61.
32. Macefield RC, Boulind CE, Blazeby JM. Selecting and measuring optimal outcomes for randomised controlled trials in surgery. *Langenbeck's Archives of Surgery* 2014; 399(3):263–72.
33. Ergina PL, Cook JA, Blazeby JM, et al. Challenges in evaluating surgical innovation. *The Lancet* 2009; 374(9695):1097–104.
34. Lingsma HF, Roozenbeek B, Li B, et al. Large Between-Center Differences in Outcome After Moderate and Severe Traumatic Brain Injury in the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) Study. *Neurosurgery* 2011; 68(3):601–8.
35. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clinical Epidemiology* 2018; 10:841–52.

PART III

CHALLENGES IN STUDYING ACUTE NEUROSURGICAL INTERVENTIONS IN TRAUMATIC BRAIN INJURY

Chapter 6

Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury

Cnossen MC, Van Essen TA, Ceyisakar IE, Polinder S, Andriessen TM, van der Naalt J, Haitsma I, Horn J, Franschman G, Vos PE, Peul WC, Menon DK, Maas AI, Steyerberg EW, Lingsma HF.

Clin Epidemiol. 2018 Jul 18;10:841-852.

ABSTRACT

Introduction: Observational studies of interventions are at risk for confounding by indication. The objective of the current study was to define the circumstances for the validity of methods to adjust for confounding by indication in observational studies.

Patients and methods: We performed post-hoc analyses of data prospectively collected from three European and North-American traumatic brain injury (TBI) studies including 1,725 patients. The effects of three interventions (intracranial pressure (ICP) monitoring, intracranial operation and primary referral) were estimated in a proportional odds regression model with the Glasgow Outcome Scale as ordinal outcome variable. Three analytical methods were compared: classical covariate adjustment; propensity score matching; and instrumental variable (IV) analysis in which the percentage exposed to an intervention in each hospital was added as an independent variable, together with a random intercept for each hospital. In addition, a simulation study was performed in which the effect of a hypothetical beneficial intervention (OR = 1.65) was simulated for scenarios with and without unmeasured confounders.

Results: For all three interventions, covariate adjustment and propensity score matching resulted in negative estimates of the treatment effect (OR ranging from 0.80-0.92), whereas the IV approach indicated that both ICP monitoring and intracranial operation might be beneficial (OR per 10% change: 1.17; 95% CI 1.01-1.42 and 1.42; 95% CI 0.95-1.97). In our simulation study, we found that covariate adjustment and propensity score matching resulted in an invalid estimate of the treatment effect in case of unmeasured confounders (OR ranging from 0.90-1.03). The IV approach provided an estimate in the similar direction as the simulated effect (OR per 10% change 1.04-1.05), but was statistically inefficient.

Conclusions: The effect estimation of interventions in observational studies strongly depends on the analytical method used. When unobserved confounding and practice variation are expected in observational multi-center studies, instrumental variable analysis should be considered.

INTRODUCTION

Randomized controlled trials (RCTs) have long been considered the cornerstone of evidence-based medicine.[1] They are however not always feasible due financial, ethical and practical constraints,[2] and are criticized for the lack of external validity.[1] Observational studies constitute the main alternative. A key challenge in observational studies of interventions is confounding by indication, a phrase that refers to a situation where patient characteristics, rather than the intervention, are independent predictors of outcome. [3] As a consequence, patients exposed and not exposed to a particular intervention might not be comparable, hampering causal inference. World leading experts in this field have stressed the need for further development and testing statistical methods to handle confounding by indication.[4-6] The epidemiological and statistical literature describes several analytical methods to account for confounding, among which covariate adjustment and propensity scores are probably the most commonly applied. In covariate adjustment, measured confounders are added as independent variables to the analytical model. This results in a risk-adjusted effect estimate.[7,8] In propensity scores, the chance ('propensity') of being exposed to the intervention, based on measured patient characteristics, is added as a covariate to the model or used to match patients exposed and not exposed.[8] Propensity scores aim to balance factors influencing management decisions[7,9,10] and are especially to be considered when there are few outcome events.[8] These commonly applied methods however, cannot adequately correct for unmeasured confounders. For example, a surgeon may decide to perform an operation because of his clinical intuition. Clinical intuition might be related to the patient's prognosis but may not be adequately captured in the clinical data and thereby may leave residual confounding.[3,11,12] A relatively new method to adjust for confounding is instrumental variable (IV) analysis. In IV, a substitute variable, 'the instrument' (e.g. hospital), is used as level of analysis. IV is becoming more popular in comparative effectiveness research (CER) and can theoretically adjust for unmeasured confounders.[7,8,13] However, its validity depends on the degree to which the following three assumptions are met: The instrument should be strongly associated with the intervention under study (assumption 1), not related to the confounders (assumption 2) and not independently associated with the outcome under study (assumption 3).[7,8,13]

Clinical practice in patients with traumatic brain injury (TBI) is generally hypothesized to be prone to confounding by indication because treatment choice and outcome are highly dependent on injury severity and clinical status. In addition, the combination of a low evidence-base and strong (cultural or eminence based) beliefs of best practice leads to large practice variation between hospitals;[14] e.g. some hospitals have the general policy to treat TBI patients (regardless of patient characteristics) with a specific intervention, whereas this intervention may only be rarely used in

other centers.[15,16] This combination makes IV analysis of observational studies in TBI a promising approach. For the purpose of the current study, we selected three interventions that have shown to be effective according to best available evidence and expert consensus meetings,[17-21] with guidelines advocating these strategies,[22-27] but also have shown extensive practice variation: ICP placement for ICP directed therapies versus serial clinical and radiological assessment,[28] to operate or not in mass lesions,[16] and primary versus secondary referral to specialized care.[27]
The objective of the current study was to define the circumstances for the validity of methods to adjust for confounding by indication using three selected interventions in TBI patients and a simulation study.

PATIENTS AND METHODS

Study populations and interventions

Three TBI datasets were used. The Prospective Observational Cohort Neurotrauma (POCON) dataset
consists of 557 consecutive patients with moderate and severe TBI (Glasgow Coma Scale (GCS) score 3-13) from five level I trauma centres in the Netherlands between 2008-2009. Detailed information on data collection, procedures and patients has been described previously.[29] From the POCON dataset, we extracted 266 patients with an indication for intracranial pressure (ICP) monitoring according to the 2007 Brain Trauma Foundation (BTF) guidelines;[30] that is, patients with a GCS ≤ 8 and a Computed Tomography (CT) Marshall score ≥ 2, or patients with a GCS score ≤ 8, CT Marshall score < 2 and at least one of the following risk factors: 1) age > 40 years; 2) hypotensive episode (SBP < 90 mmHg); and 3) motor score ≤ 3 (unilateral of bilateral motor posturing).
We further used the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) dataset, which consists of data from prospective studies and phase III trials in patients with moderate and severe TBI.[31] The International and North American Tirilazad trial (86 hospitals between 1992 and 1994) was selected from the IMPACT dataset, because it comprises the requisite data to estimate the effectiveness of intracranial operations (craniotomy or craniectomy). From the 2,159 patients included in this trial, data of 677 patients with severe TBI, a mass lesion and a six-month outcome assessment were extracted.
We additionally selected the European Brain Injury Consortium (EBIC) study (67 hospitals, in 1995) from the IMPACT dataset, which contains information on referral status of 822 patients. Referral and outcome were assessed in 782 patients, who were subsequently extracted. Detailed information on the IMPACT dataset has been

comprehensively described in previous publications.[31-33] The POCON, Tirilazad and EBIC studies were approved by the institutional review boards of the participating centers and all patients provided informed consent. Data was made available for the current study after an agreement with the principal investigators of these studies.

Data collection

Collected patient variables in all datasets included age, sex, GCS (motor) score, pupillary reactivity (both pupils reactive, one pupil reactive, no pupil reactivity), hypoxic episode (at injury scene or emergency department), hypotensive episode (at injury scene or emergency department), admission glucose level (mmol/L) and admission hemoglobin level (hb, g/L). In all datasets, the initial CT scan was assessed using the Marshall score,[34] and the presence of traumatic subarachnoid hemorrhages (tSAH) and epidural hemorrhages (EDH) were scored.

To summarize patient characteristics, we calculated the probability of survival and favourable outcome (Glasgow Outcome Scale (GOS) score ≥4) for each patient based on the IMPACT laboratory model[35] with all above-mentioned demographic and clinical factors as predictors. These prognostic scores reflect chances on respectively survival and favourable outcome based on baseline characteristics.

Six-month outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E) in the POCON dataset and the GOS in the EBIC and Tirilazad trial datasets. Both scales were collapsed into a four-point ordinal scale: 1= death or persistent vegetative state; 2 = severe disability; 3 = moderate disability; 4 = good recovery.

Statistical analyses

Missing values in patient characteristics were imputed using single imputation. To assess differences in patient characteristics between patients exposed and not exposed to the interventions in the imputed datasets, we compared these characteristics in terms of clinical relevancy.

To examine the effectiveness of interventions, we used proportional odds logistic regression models with the 4-point ordinal GOS as outcome variable. A proportional odds model increases statistical power in comparison to a conventional logistic regression model with a binary outcome.[36] The odds ratios (OR) derived from a proportional odds regression model could be interpreted as the average shift over the GOS caused by the intervention under study.[36]

As a reference, we estimated unadjusted effects of the interventions with patient (exposed to the intervention yes/no) as the unit of analysis. To adjust for confounders, we performed covariate adjustment, propensity score matching and IV analysis. In the covariate-adjusted model, the variables from the IMPACT prognostic model[35] (age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification,

tSAH, EDH, glucose and Hb) were added as independent variables. In a propensity score model, the propensity of being exposed to the intervention was computed using multivariable logistic regression with the intervention under study as dependent variable and all IMPACT variables as predictors. Propensity score matching was used to match patients who were exposed to the intervention to patients who were not exposed to the intervention with a maximum difference of 0.10 between propensity scores. An advantage of propensity score matching is that patients with non-overlapping propensity scores are omitted from the analyses, increasing the comparability of those exposed and not exposed.[7,9] In addition, propensity score matching is relatively robust and relies on fewer assumptions than other propensity score-based methods (e.g. propensity score adjustment).[37]

We used fixed effect models for all patient-level analyses. The ORs and 95% confidence intervals (CIs) were obtained from the models and the ORs indicated the odds of a more favourable outcome for patients who were exposed to the intervention compared to patients not exposed.

For the IV analyses, we entered the percentage exposed to the intervention in each hospital (the instrument) as an independent variable to the analyses, together with a random intercept for hospital to correct for other between-hospital differences than the intervention under study or between-hospital differences that existed by chance. All IMPACT prognostic variables were added as covariates to increase statistical power.[38] To minimize the influence of chance, we only included hospitals with data on at least 20 patients in the IV analyses. The ORs were obtained from the models and the corresponding 95% CIs were calculated using bootstrapping with 500 samples. The ORs indicated the odds on a more favourable outcome for a 10% increase in exposure to the intervention in a particular hospital. Assumptions of the IV approach were checked by calculating the partial F statistic, in line with recommendations.[39] In addition, we checked associations with measured confounders by calculating Spearman's correlation coefficients between the instrumental variables and the prognostic scores of survival and favourable outcome. The third assumption (the instrumental variable is not independently associated with outcome) cannot be empirically verified, but is captured in the random effect model that we used.

The proportional odds analyses were performed in R (version 3.1.2) using the *ordinal* package.[40] Other analyses were performed using the Statistical Package for the Social Sciences version 21.

Sensitivity analyses

As sensitivity analyses we explored alternative methods for propensity score matching and IV analysis. Since propensity score matching may result in a non-representative sample[7] and a loss of statistical power,[41] we also used propensity

score adjustment and inverse probability weighting (IPW) to estimate the treatment effect. For propensity score adjustment, the linear predictor of the propensity score was added as a covariate to the proportional odds regression models. In IPW, the outcome of patients exposed to the intervention is extrapolated to the non-exposed patients with similar propensity scores; for every patient exposed with a probability of 0.20, there are four patients with the same probability who were not exposed. The outcome of the exposed patient is subsequently extrapolated to all other four patients with the same propensity score.[42] We used standardized weights in which we divided the unadjusted chance of receiving the intervention in the total study population by the propensity score.[43] Since this still resulted in large standard errors, we winsorized our cohort by 95%; i.e. patients below the 2.5th and above the 97.5th percentile received the scores belonging to the 2.5th and 97.5th quartile, respectively.
As an alternative to the IV approach used in this study, we divided hospitals into two groups based on their preference for the intervention. The mean percentage exposed to each intervention was calculated and hospitals scoring above these means were classified as having a high preference, whereas hospitals scoring below the means were classified as having a low preference.
Since the percentage patients exposed to the intervention in each hospital can still be based on case-mix (e.g. in a hospital with more severely injured patients, the percentage patients receiving aggressive interventions might be higher) and could also exist by chance, we estimated a random intercept for hospital from a model predicting exposure to the intervention yes/no adjusted for the IMPACT variables. This random intercept for exposure represents the chance of receiving the intervention in a specific hospital corrected for case-mix and chance, and was subsequently used instead of the percentage exposed in the IV analyses. A disadvantage of this method is that the estimate obtained is hard to interpret and very uncertain due to the shrinkage of the between-hospital variation by the random effects model.

Simulation study

In empirical data, 'true' effects are never known and as a consequence, estimating the validity of analytical methods remains difficult. Therefore, we performed a simulation study in which a true treatment effect was simulated in the data. The simulation study was built around the POCON dataset, which was inflated to 133,000 patients from 20 hospitals. We simulated a hypothetical intervention with a beneficial effect of OR = 1.65. For the association between the hypothetical intervention and confounders, we used the observed associations between ICP monitoring and confounders in the POCON dataset. We used six-month survival (yes/no) as outcome variable, which was generated based on a combination of the prognostic effect of the confounders and the effect of the hypothetical intervention.

We simulated four different scenarios and estimated the treatment effect using covariate adjustment, propensity score matching and IV analysis. In the first scenario, there were only measured confounders. We used motor score and pupillary reactivity as representing the measured confounders. In the second scenario, both measured and unmeasured characteristics comprised confounders. Marshall CT scores and the presence of a tSAH were used as unmeasured confounders. For both the first and second scenario, no between-hospital variation existed, which is comparable to a single-center study. The third and fourth scenarios were similar to the first and the second, but included between-hospital variation in how often the hypothetical intervention was performed. Since the observed variation of ICP monitoring among hospitals ranged from 17 to 58%, every hospital received a random percentage within this range. The simulations were performed in R statistical software using the *rms*[44] and *lme4*[45] packages.

RESULTS

Patient characteristics

In the POCON dataset (n = 266), used for exploring the effects of ICP monitoring, patients who received an ICP monitor (n = 110) were generally younger, more often male, had a lower GCS motor score, less pupillary reactivity, less often hypoxia and hypotension and more often a mass lesion. In addition, patients receiving an ICP monitor more often had tSAH, EDH, and had on average a higher glucose level. These baseline differences resulted in a worse *a priori* prognosis for patients who received an ICP monitor compared to patients who did not receive an ICP monitor (n = 156; chance on survival 39% and 58% respectively). Observed outcome was also less favourable in patients who received an ICP monitor.

In the Tirilazad dataset (n = 677), used for exploring the effects of intracranial surgery, patients who did (n = 579) and did not (n = 98) receive an intracranial operation did not differ on baseline characteristics except for hypotension (14% vs 21%,) and the presence of an EDH (31% vs 10%,), nor did the observed outcome differ.

In the EBIC dataset (n = 782), used for exploring the effects of referral policy, patients who were primary referred (n = 334) had higher blood glucose levels (8.1 vs. 7.9 mmol/L) and more often a tSAH (47% vs. 38%) compared to patients who were secondary referred (n = 448). There were no other clinical meaningful differences between groups (Table 1).

Table 1. Baseline, clinical and outcome characteristics of patients exposed and not exposed to three interventions

Characteristic	POCON dataset		Tirilazad dataset		EBIC dataset	
	ICP+ (n = 110)	ICP- (n = 156)	Intr. Operation+ (n = 579)	Intr. Operation- (n = 98)	Primary Ref. (n = 334)	Secondary Ref. (n = 448)
Age (median, IQR)	45 (27-57)	58 (35-70)	35 (24-47)	33 (25-47)	33 (22-53)	41 (26-60)
Male sex	79 (72%)	99 (64%)	463 (80%)	78 (80%)	245 (73%)	337 (75%)
GCS motor score (median, IQR)	1 (1-1)	1 (1-3)	4 (3-5)	4 (3-5)	5 (2-6)	5 (2-6)
Pupillary reactivity						
-Both pupils reactive	48 (44%)	93 (60%)	346 (60%)	57 (58%)	213 (64%)	298 (66%)
-One pupil reactive	13 (12%)	14 (9%)	106 (18%)	18 (18%)	30 (9%)	44 (10%)
-No pupil reactive	49 (44%)	49 (31%)	127 (22%)	23 (24%)	91 (27%)	106 (24%)
Hypoxia (yes or suspected)	24 (22%)	50 (32%)	115 (20%)	25 (26%)	93 (28%)	132 (30%)
Hypotension (yes or suspected)	22 (20%)	55 (35%)	80 (14%)	21 (21%)	87 (26%)	104 (23%)
CT classification†						
-Normal	2 (2%)	26 (16%)	NA	NA	49 (15%)	46 (10%)
-Diffuse II	25 (23%)	64 (41%)	NA	NA	102 (31%)	125 (28%)
-Diffuse III/IV	19 (17%)	15 (10%)	NA	NA	45 (14%)	52 (12%)
-Mass lesion	64 (58%)	51 (33%)	579 (100%)	98 (100%)	138 (41%)	225 (50%)
tSAH	70 (64%)	77 (49%)	319 (55%)	56 (57%)	156 (47%)	168 (38%)
EDH	19 (17%)	10 (6%)	178 (31%)	10 (10%)	30 (%)	44 (10%)
Glucose (mmol/L) (median, IQR)	9.0 (7.3-11.1)	8.3 (6.7-11.0)	8.4 (6.9-10.8)	8.4 (6.5-10.8)	8.1 (6.8-10.9)	7.9 (6.4-9.6)
Hemoglobin (g/dL) (mean, IQR)	7.5 (6.3-8.3)	7.6 (6.6-8.5)	12.8 (11.0-14.3)	13.2 (11.1-14.8)	12.7 (11.0–14.4)	12.9 (11.3–14.3)
$P_{survival6}$‡	.39 (.15-.77)	.58 (.12-.92)	.74 (.52-.86)	.75 (.47-.85)	.75 (.38-.92)	.79 (.44-.93)
P_{fav6}‡	.16 (.06-.41)	.40 (.05-.78)	.49 (.23-.72)	.53 (.19-.71)	.49 (.19 - .76)	.53 (.22-.78)

Table 1. Baseline, clinical and outcome characteristics of patients exposed and not exposed to three interventions (*continued*)

Characteristic	POCON dataset		Tirilazad dataset		EBIC dataset	
	ICP+ (n = 110)	ICP- (n = 156)	Intr. Operation+ (n = 579)	Intr. Operation- (n = 98)	Primary Ref. (n = 334)	Secondary Ref. (n = 448)
GOS						
-Death	60 (54%)	73 (47%)	190 (33%)	37 (38%)	116 (35%)	146 (32%)
-Persistent vegetative state	2 (2%)	0 (0%)	36 (6%)	3 (3%)	11 (3%)	7 (2%)
-Severe disability	20 (18%)	16 (10%)	77 (13%)	8 (8%)	46 (14%)	68 (15%)
-Moderate disability	22 (20%)	26 (17%)	85 (15%)	20 (20%)	70 (21%)	85 (19%)
-Good recovery	6 (6%)	41 (26%)	191 (33%)	30 (31%)	91 (27%)	142 (32%)

Notes: Table presents values after data imputation. Values are presented as n (%) unless otherwise specified. P-values represent the differences between patients receiving and not receiving the intervention.

† CT classification is based on the Marshall classification. Diffuse II refers to CT abnormalities without swelling or shift; Diffuse III refers to CT abnormalities with swelling (compressed cisterns); Diffuse IV refers to CT abnormalities with a shift. ‡ $P_{survival6}$ is the probability of 6-month survival; P_{fav6} is the probability of 6-month favorable outcome (GOS ≥ 4). The probabilities are based on the variables in the IMPACT lab model[35]; age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, SAH, EDH, Glucose and Hemoglobin.

Abbreviations: CT = Computed Tomography; EBIC = European Brain Injury Consortium; ED = Emergency Department; EDH = Extradural Hematoma; GOS = Glasgow Outcome Scale; GCS = Glasgow Coma Scale; ICP+ = patients receiving Intracranial Pressure monitoring; ICP- = patients not receiving Intracranial Pressure monitoring; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in TBI; Intr. Operation+ = patients receiving intracranial operation (Craniotomy or craniectomy); Intr. Operation- = patients not receiving intracranial operation (Craniotomy or craniectomy); ISS = Injury Severity Score; IQR = Interquartile range; POCON = Prospective Observational Cohort Neurotrauma Study; Ref = referral; tSAH = traumatic Subarachnoid Hematoma.

Table 2. Comparing analytical methods to adjust for confounding by indication in proportional odds logistic regression models with the Glasgow Outcome Scale as outcome

Approach	POCON dataset ICP monitoring OR (95% CI)	Tirilazad dataset Intracranial operation OR (95% CI)	EBIC dataset Primary referral OR (95% CI)
Unadjusted model	0.51 (0.32-0.81)	1.04 (0.70-1.54)	0.85 (0.66 – 1.10)
Covariate adjustment*	0.91 (0.48-1.74)	0.92 (0.59-1.42)	0.85 (0.64 – 1.15)
Propensity score matching**	0.80 (0.42-1.54)	0.89 (0.53-1.50)	0.89 (0.76 -1.18)
Hospital-level approach†	1.17 (1.01-1.42)	1.42 (0.95-1.97)ł	0.91 (0.81 – 1.03)Ł

Notes: *Model was adjusted for the following confounders: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin

**A propensity score was calculated based on the following variables: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin. For ICP monitoring, matching resulted in 67 patients receiving the intervention (propensity score 0.47, probability on survival 0.46, probability on favorable outcome 0.28) and 67 patients not receiving the intervention (propensity score 0.46, probability on survival 0.43, probability on favorable outcome 0.32). For craniotomy, matching resulted in 96 patients receiving the intervention (propensity score 0.83, probability survival 0.63, probability favorable outcome 0.42) and 96 patients not receiving the intervention (propensity score 0.83, probability survival 0.63, probability favorable outcome 0.42). For primary referral, matching resulted 312 patients primary referred (propensity score 0.46; probability survival 0.65; probability favorable outcome 0.49) and 312 patients secondary referred (propensity score 0.47, probability survival 0.65, probability favorable outcome 0.48).

†Per 10% change; Model was adjusted for the following confounders: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin

łAnalyses in 7 centers with a total of 172 patients

ŁAnalyses in 12 centers with a total of 350 patients

Abbreviations: CT, computed tomography; EBIC, European Brain Injury Consortium; EDHs, epidural haemorrhages; GCS, Glasgow Coma Scale; ICP, intracranial pressure; POCON, Prospective Observational Cohort Neurotrauma; tSAHs, traumatic subarachnoid hemorrhages.

Covariate adjustment and propensity score matching

Unadjusted analyses showed that patients receiving an ICP monitor in the POCON dataset had a worse outcome than patients not receiving an ICP monitor (OR 0.51; 95%CI 0.32-0.81; Table 2). For intracranial operation and primary referral, as analysed in the Tirilazad and EBIC datasets respectively, only minor differences were found between treated and non-treated patients. Covariate adjustment and propensity score matching resulted in imprecise estimates below one, indicating that exposure to the interventions might have either a negative or no effect on outcome.

Instrumental variable analysis

In the POCON dataset, the percentage of patients that received an ICP monitor ranged from 17-58% between participating hospitals. All five hospitals included at least 20 patients (range 37-51 patients). For intracranial operation, only seven

Table 3. Comparing analytical methods to adjust for confounding by indication in a simulation study with 6 month survival as binary outcome

Approach	Scenario 1* OR (95% CI)	Scenario 2* OR (95% CI)	Scenario 3* OR (95% CI)	Scenario 4* OR (95% CI)
Unadjusted model	1.02 (1.00-1.04)	0.69 (0.68-0.71)	0.96 (0.93-0.98)	0.72 (0.70-0.74)
Covariate adjustment	1.67 (1.63-1.71)	0.99 (0.97-1.02)	1.52 (1.47-1.56)	1.03 (1.00-1.06)
propensity score matching	1.46 (1.43-1.50)	0.90 (0.88-0.92)	1.46 (1.41-1.50)	0.94 (0.91-0.97)
Hospital-level approach†	NA	NA	1.05 (1.04-1.07)	1.04 (1.02-1.05)

Notes: *Scenario 1 = observed confounders, no hospital variation; Scenario 2 = observed and unobserved confounders, no hospital variation; scenario 3 = observed confounders, hospital variation (17-58%), scenario 4 = observed and unobserved confounders, hospital variation (17-58%)
†Per 10% change

hospitals from the Tirilazad dataset included more than 20 patients, encompassing 172 patients. The percentage of patients receiving an intracranial operation ranged from 67 to 100% between hospitals. For primary referral, 12 hospitals from the EBIC dataset included more than 20 patients, reducing the sample size to 350 patients. The percentage primary referrals ranged from 17 to 83% between hospitals.
The instruments (percentage of patients exposed to the intervention in each hospital) were associated with the interventions under study (Partial F statistic 6.96 to 65.9). In addition, correlations between the instruments and confounders were generally small (Online supplement 1), indicating that the assumptions for IV analyses are met Using IV analysis, we found that patients treated in hospitals that performed 10% more ICP monitors had an 1.17 (95% CI 1.01-1.42) higher odds on favorable outcome, compared to patients treated in hospitals where ICP monitoring was less often employed (Table 2). For intracranial operation, a 10% increase resulted in a higher odds of favorable outcome, but this estimate was rather imprecise (OR 1.42, 95% CI 0.95-1.96). For primary referral, centers admitting more primary referred patients and less secondary referred patients had a slightly worse outcome (OR: 0.91, 95% CI 0.81-1.03). More primary referrals and consequently less secondary referrals are indicative for less specialized neurocritical care, and therefore, an odds ratio below one was in line with expectations.

Sensitivity analyses

Propensity score adjustment and IPW resulted in similar effect estimates compared to covariate adjustment and propensity score matching (Online Supplement 2). The alternative hospital-level approaches resulted in effect estimates in the same direction as the IV analyses. Confidence intervals were however large, indicating a decrease of statistically efficiency.

Table 4. Characteristics of analytical methods to adjust for confounding by indication based on our simulation- and validation study

Approach	Adjustment for measured confounders	Adjustment for unmeasured confounders	Statistical efficiency	Relying on strong assumptions	Interpretation
Unadjusted model	-	-	+	-	+
Covariate adjustment	+	-	+/- ł	-	+
Propensity score matching	+	-	-	-	+
Instrumental variable analysis	+	+*	-	+	-

Notes: ł Statistical efficiency depends on the number of covariates and the number of patients with the outcome of interest ('events').
*In theory, instrumental variable analysis can correct for unmeasured confounders.

Simulation study

The unadjusted analyses resulted in ORs ranging from 0.69 to 1.02 for the four different scenarios (Table 3). In the scenarios where the associations between intervention and outcome were influenced by measured confounders only (scenario 1 and 3), covariate adjustment and propensity score matching resulted in ORs in the range of 1.46-1.67, broadly in line with the simulated effect (OR = 1.65). However, in the scenarios where unmeasured confounders also influenced the association between intervention and outcome (scenario 2 and 4), the adjusted ORs in multivariable analyses were all close to the point of no effect (OR 0.99 and 1.03), whereas the ORs in the propensity-score matching models were negatively directed (OR 0.90 and 0.94). IV analysis resulted in a positive and statistically significant effect (OR 1.04-1.05 per 10% change), indicating that patients admitted to hospitals that more often performed the hypothetical intervention had better odds on survival than patients admitted to hospitals where the intervention was less often performed. When transforming these ORs to a 100% change (meaning that all patients in a center would receive the hypothetical treatment), the effect estimate (OR = 1.05^10 = 1.63) is highly comparable to the simulated treatment effect. The standard errors of the hospital-level analyses (SE 0.07) were however far larger than the standard errors in the patient-level analyses (SE 0.01), indicating a substantial reduction in statistical efficiency (Table 4).

DISCUSSION

We compared analytical methods to adjust for confounding by indication in observational studies using three empirical case studies and a simulation study. The estimated effects strongly depended on the analytical method applied. As expected, the presence of unmeasured confounders, makes covariate adjustment and propensity score matching invalid. Instrumental variable (IV) analysis, although statistically inefficient and relying on strong assumptions, may then provide more valid estimates of the effectiveness of interventions.

Covariate adjustment and propensity score matching

Covariate adjustment and propensity score matching are commonly used in observational studies of interventions. We found that these methods could provide an unbiased estimate of the effect of the intervention, on the condition that all relevant confounders are measured and adjusted for. Covariate adjustment and propensity score matching cannot adjust for unmeasured confounders.[3,7,11,12,41] In our simulation study, for example, the beneficial interventions appeared harmful or non-effective when analyzed with covariate adjustment or propensity score matching, due to residual confounding by indication.

Instrumental variable analysis

IV analysis resulted in better estimates of the effect of interventions in our simulation study; the direction of the effect was congruent with the simulated effect. In our empirical case studies, the directions of effects were in line with how patients should be treated according to guidelines for TBI[22-26] and best available evidence.[17,26,27,46]

IV analysis is becoming more popular in TBI research. Several recently published TBI studies analysed effectiveness at the hospital level[47-50] and a large European CER study is planning to use hospital-level analysis to assess effectiveness of many TBI interventions.[51] Previous studies typically divided hospitals into groups (e.g. tertiles[47] or quartiles[48]) based on the percentage of patients treated. The percentage treated in each hospital can also be used as a continuous variable, which increases statistical power.

Nevertheless, IV analysis also has limitations that warrant comment. First, IV analysis is statistically inefficient compared to conventional analytical methods. Since the analyses are performed at the level of the hospital, the effective sample size decreases. As a consequence, a large number of centers and patients and substantial variability in exposure to interventions across centers are needed to reach a precise estimate in case of a true beneficial effect. The conduct of IV analysis might therefore be relatively expensive and resource-intensive. However, when compared to clinical

trials, IV analysis of observational data is probably more economical since many research questions could be addressed using the same data.
Second, the interpretation of the OR differs from the conventional analyses. Rather than an estimate of the effect of interventions in individual patients, IV provides information on whether patients' outcome will improve when hospitals change their policy with respect to a specific intervention.[7-9] The issue of interpretation is prominent for primary referral. Although primary referral on the patient-level might be associated with more specialized neurocritical care, at the hospital-level a larger number of primary referrals and thus a lower number of secondary referrals are indicative for less specialized care. Therefore, for primary referral, a negative association between the instrument 'percentage primary referrals' and outcome was expected, which was indeed found in the EBIC data. Third, the success of IV analysis depends on whether the underlying assumptions are met.[9,52,53] Thus, IV analysis might not always be defendable. Between-hospital variation, caused by other variables than those in the model, could theoretically be captured by the random effect model. Nevertheless, when correlations are strong (e.g. centers that often perform a particular intervention are all from the same geographic region that differs from other regions in many aspects), the statistical model will be unable to separate the effect of the intervention from the effect of the confounder. In these situations, one should consider other analytical methods or conclude that it is not possible to analyze the effectiveness of the particular intervention in the dataset.

Strengths and Limitations

A major strength of our study is that we included both empirical case studies and a simulation. The TBI examples show how the various analytical methods worked with actual patient data and demonstrated the influence of analytical method on effect estimate. The simulation study subsequently provided insight into the underlying mechanisms and thereby indicated which methods provided valid estimates of the treatment effect in different situations. A limitation of our simulation study is that we only examined four scenarios while there are many more possible interactions between treatment and confounders that might be of interest. A second limitation is that we used the observed range from one dataset (POCON), whereas the actual range might differ. Future simulation studies could address alternative scenarios and should further investigate how statistical power can be optimized when using IV analysis. Another limitation of the simulation study is that we included two variables as presenting the measured confounders and two variables as presenting the unmeasured confounders. As a consequence, the predictive value of our predictors is relatively modest which may have resulted in unstable estimates.

Our case studies also have several limitations. The data is relatively outdated (data was collected between 1992 and 2009) and analyzed post-hoc. Therefore, the current study cannot be used to draw conclusions about the effectiveness of interventions. In addition, each intervention was measured in only one dataset while it would be more interesting to demonstrate the different analytical methods for each intervention over different datasets. This was not possible in our study since not all interventions were measured in all three datasets. Furthermore, specific concerns exist in the data with regard to the three interventions. An ICP monitor is a diagnostic procedure and cannot influence outcome on itself, while it can cause complications. The actual comparison is between ICP driven therapies versus clinical/radiological driven therapies. With regard to the variable intracranial operation, the clinical applicability is unclear since the exposure and intervention in these data are not defined specifically (What kind of mass lesions? What intracranial operation?). More granular information on these interventions was unavailable inherent to the post-hoc setup. For primary referral, we assumed that more primary referrals are associated with less specialized care. However, an alternative explanation would be that many primary referrals in a center are indicative that this center has a central location.. Another limitation is that all three datasets were relatively modest in terms of number of hospitals and number of patients. The POCON dataset had only five hospitals, while the Tirilazad and EBIC datasets had only seven and 12 hospitals that included at least 20 patients, respectively. Therefore, differences among hospitals might also exist by chance; for instance, if a hospital included only 20 patients, these patients might not be representative for the general policy in the particular hospital. Therefore, we recommend future studies using IV analyses in TBI to include a larger number of hospitals and a large number of patients in each hospital. In addition, since the 'percentage treated' in each hospital is based on data of the included patients, it might still be subject to confounding by indication. Alternatively, policies with regard to an intervention might be identified by (former) registry data or by an independent survey study completed by all the participating hospitals. Such an approach will be used in an ongoing TBI study.[51] A further limitation may have been the use of an ordinal outcome measurement. Although ordinal outcome measurements are highly recommended in TBI research due to an increase of statistical power and precision,[36] it is uncertain whether the results of this study are also generalizable to binary and continuous outcomes. Finally, it should be recognized that all covariates included in this study are measured only at admission, while the clinical situation of a patient may change over time (e.g. the GCS score may deteriorate), resulting in a different risk profile and also influencing treatment decisions. Allowing time-varying aspects may probably improve the predictive value of covariates and thereby may also improve the validity of patient-level analyses, This should be studied in

future investigations. although it should be noted that only covariates that are known before the treatment decision is made are relevant, to avoid over-adjustment.

Implications

IV is emerging as an analytical method in many research fields, including oncology,[54] cardiovascular disease[55] and pharmaco-epidemiology.[56] We demonstrated that IV might provide a more valid estimate of the treatment effect compared to conventional analytical methods. In addition, IV is not only suitable for analyzing the effectiveness of individual interventions, but can also be applied to estimate the effectiveness of systems of care; for instance, Pezzin and colleagues[57] studied the influence of volume on breast cancer mortality using IV. We showed that the percentage treated in each hospital might be a valid instrument. Notwithstanding, for interventions that show mainly between-region or between-country variation rather than between-hospital variation, e.g. prehospital trauma care, one might choose to analyze the results on the level of the region or country rather than the level of the hospital. Since all methods for causal inference have their strengths and limitations, it is nevertheless not desirable to regard one method as 'correct'.[58] Instead, alternative methods should be used simultaneously.[58] In case alternative method provide similar results, the credibility of the findings may strengthen. However, if findings are non-concordant one has to determine which method is the most credible. Laborde-Casterot and colleagues[59] developed a flow-chart to determine which method (IV vs. patient-level methods) may provide the most valid results. Factors that could be taken into account when analyzing non-concordance of result include the risk of confounding by indication, the strength of the instrument, the validity of the instrument, the statistical power and concordance with RCTs on the same intervention (if available).[59]

CONCLUSION

The effect estimation of interventions in observational studies strongly depends on the analytical method used. When unobserved confounding and practice variation are expected in observational multi-center studies, instrumental variable analysis should be considered.

ABBREVIATIONS

CER	Comparative effectiveness research
CI	Confidence interval
CT	Computed tomography
GCS	Glasgow coma scale

GOS	Glasgow outcome scale
GOSE	Glasgow outcome scale extended
EBIC	European brain injury consortium
EDH	Epidural hemorrhages
ICP	Intracranial pressure
IMPACT	International mission for prognosis and analysis of clinical trials
IPW	Inverse probability weighting
IV	Instrumental variable
OR	Odds ratio
POCON	Prospective observational cohort neurotrauma study
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SE	Standard error
TBI	Traumatic brain injury
TSAH	Traumatic subarachnoid hemorrhages

AUTHORS' CONTRIBUTIONS

HL invented the idea for this paper. MC, TvE, IC and HL analyzed the data. MC and TvE wrote the manuscript. JvdN and PV collected the data for the POCON study. AM, JvdN and PV were involved in the data collection for the IMPACT study. All authors were involved in critically revising the manuscript and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

This work was funded by the European Union PF 7th Framework program (grant 602150) – CENTER TBI. In addition, the author Thomas van Essen was funded by a grant from the Dutch Brain Foundation (Hersenstichting Nederland) for the Neurotraumatology Quality Registry (Net-QuRe) study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DISCLOSURE

No competing interests exists.

REFERENCES

1. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. *N Engl J Med* 2017; 377(5):465-475.
2. Maas AI, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. *J Neurotrauma* 2012; 29(1):32-46.
3. Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther* 2002; 9(3):199-205.
4. Ioannidis JPA, Khoury MJ. Improving validation practices in "omics" research. *Science* 2011;334(6060):1230-1232.
5. Normand SLT, McNeila BJ. What is evidence? *Statistics in Medicine* 2010; 29(19):1985-1988.
6. Basch E, Aronson N, Berg A, et al. Methodological standards and patient-centeredness in comparative effectiveness research: The PCORI perspective. *JAMA* 2012; 307(15):1636-1640.
7. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; 297(3):278-285.
8. Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted Analyses in Studies Addressing Therapy and Harm: Users' Guides to the Medical Literature. *JAMA* 2017; 317(7):748-759.
9. Hiatky MA, Winkelmayer WC, Setoguchi S. Epidemiologic and statistical methods for comparative effectiveness research. *Heart Fail Clin* 2013; 9(1):29-36.
10. Austin PC, Mamdani MM, Stukel TA, et al. The use of the propensity score for estimating treatment effects: Administrative versus clinical data. *Stat Med* 2005; 24(10):1563-1578.
11. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010; 63(1):64-74.
12. Sjoding MW, Luo K, Miller MA, Iwashyna TJ. When do confounding by indication and inadequate risk adjustment bias critical care studies? A simulation study. *Crit Care* 2015; 19:195.
13. Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: Assessing validity and interpreting results. *Int J Biostat* 2007; 3(1).
14. Rayan N, Barnes S, Fleming N, et al. Barriers to compliance with evidence-based care in trauma. *J Trauma Acute Care Surg* 2012; 72(3):585-592; discussion 592-583.
15. Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Crit Care* 2017; 21(1):233.
16. Van Essen TA, De Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; 34(4):881-889.
17. Yuan Q, Wu X, Sun Y, et al. Impact of intracranial pressure monitoring on mortality in patients with traumatic brain injury: a systematic review and meta-analysis. *J Neurosurg* 2015;122(3):574-587.
18. Chesnut RM, Bleck TP, Citerio G, et al. A Consensus-Based Interpretation of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure Trial. *Journal of Neurotrauma* 2015; 32(22):1722-1724.
19. Mendelow AD, Gregson BA, Rowan EN, et al. Early Surgery versus Initial Conservative Treatment in Patients with Traumatic Intracerebral Hemorrhage (STITCH[Trauma]): The First Randomized Trial. *Journal of Neurotrauma* 2015; 32(17):1312-1323.
20. Seelig JM, Becker DP, Miller JD. Traumatic acute subdural hematoma. Major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304(25):1511-1518.
21. Arthur KR, Kelz RR, Mills AM, et al. Interhospital transfer: an independent risk factor for mortality in the surgical intensive care unit. *Am Surg* 2013; 79(9):909-913.
22. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; 80(1):6-15.
23. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006; 58(SUPPL. 3):S225-S246.
24. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural

hematomas. *Neurosurgery* 2006; 58(SUPPL. 3):S216-S224.
25. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute epidural hematomas. *Neurosurgery* 2006; 58(SUPPL. 3):S27-S215.
26. National Institute for Health and Care Excellence (NICE). Head injury: Assessment and early management, clinical guideline (cg 176). 2014; nice.org.uk/guidance/cg176. Accessed 13 October, 2016.
27. Härtl R, Gerber LM, Iacono L, Ni Q. Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. *The Journal of Trauma* 2006; Jun;60(6):1250-6;
28. Bulger EM, Nathens AB, Rivara FP, et al. Management of severe head injury: institutional variations in care and effect on outcome. *Crit Care Med* 2002;30(8):1870-1876.
29. Andriessen TM, Horn J, Franschman G, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma* 2011;28(10):2019-2031.
30. Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury 2007; 24.http://www.braintrauma.org/pdf/protected/Guidelines_Management_2007w_bookmarks.pdf http://online.liebertpub.com/doi/pdfplus/10.1089/neu.2007.9999. Accessed June 3th 2014.
31. Marmarou A, Lu J, Butcher I, et al. IMPACT database of traumatic brain injury: Design and description. *J Neurotrauma* 2007;24(2):239-250.
32. Murray GD, Butcher I, McHugh GS, et al. Multivariable prognostic analysis in traumatic brain injury: Results from the IMPACT study. *J Neurotrauma* 2007; 24(2):329-337.
33. Maas AI, Marmarou A, Murray GD, Teasdale SG, Steyerberg EW. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. *J Neurotrauma* 2007;24(2):232-238.
34. Marshall LF, Marshall, S.B., Klauber, M.R., Berkum Clark, M. et al. A new classification of head injury based on computerized tomography. *J. Neurosurgery* 1991;75(November, 1991):S14-S20.
35. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; 5(8):e165; discussion e165.
36. Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: An example in traumatic brain injury. *Crit Care* 2011; 15(3).
37. Williamson E, Morley R, Lucas A, Carpenter J. Propensity scores: from naive enthusiasm to intuitive understanding. *Stat Methods Med Res* 2012; 21(3):273-293.
38. Roozenbeek B, Maas AI, Lingsma HF, et al. Baseline characteristics and statistical power in randomized controlled trials: selection, prognostic targeting, or covariate adjustment? *Crit Care Med* 2009; 37(10):2683-2690.
39. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363-369.
40. Ordinal – Regression Models for Ordinal Data [computer program]. 2015. Available from: https://cran.r-project.org/web/packages/ordinal/ordinal.pdf. Accessed December 01, 2016.
41. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J* 2011; 32(14):1704-1708.
42. Halpern EF. Behind the numbers: Inverse probability weighting. *Radiology* 2014; 271(3):625-628.
43. Moodie EE, Stephens DA. Marginal Structural Models: unbiased estimation for longitudinal studies. *Int J Public Health* 2011; 56(1):117-119.
44. Harrell F.E. Package 'rms'. 2017; https://cran.r-project.org/web/packages/rms/rms.pdf.
45. Bates D, Maechler, M., Bolker, B., & Walker, S. lme4: Linear mixed-effect models using Eigen and S4. R package version 1.1-8 ed2015.
46. Gregson BA, Rowan EN, Francis R, et al. Surgical trial in traumatic intracerebral haemorrhage (STITCH): A randomised controlled trial of early surgery compared with Initial conservative treatment. *Health Technology Assessment* 2015; 19(70):1-138.
47. Dawes AJ, Sacks GD, Cryer HG, et al. Compliance With Evidence-Based Guidelines and Interhospital Variation in Mortality for Patients With Severe Traumatic Brain Injury. *JAMA Surg* 2015;150(10):965-972.
48. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *J Neurotrauma* 2013; 30(20):1737-1746.

49. Hartings JA, Vidgeon S, Strong AJ, et al. Surgical management of traumatic brain injury: A comparative-effectiveness study of 2 centers: Clinical article. Journal of *Neurosurgery* 2014; 120(2):434-446.
50. Van Essen TA DM, Cnossen MC, et al. Comparative effectiveness of surgery for acute subdural hematoma. *J Neurotrauma* 2016; A20-A20.
51. Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study. *Neurosurgery* 2015; 76(1):67-80.
52. Hernan MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology* 2006; 17(4):360-372.
53. Swanson SA, Miller M, Robins JM, Hernan MA. Definition and evaluation of the monotonicity condition for preference-based instruments. *Epidemiology* 2015;26(3):414-420.
54. Xu JC, Shen J, Shao WZ, et al. The safety and efficacy of levetiracetam versus phenytoin for seizure prophylaxis after traumatic brain injury: A systematic review and meta-analysis. *Brain injury* 2016:1-8.
55. Sanwald A, Schober T. Follow Your Heart: Survival Chances and Costs after Heart Attacks-An Instrumental Variable Approach. *Health Serv Res* 2017; 52(1):16-34.
56. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; 19(6):537-554.
57. Pezzin LE, Laud P, Yen TW, et al. Reexamining the Relationship of Breast Cancer Hospital and Surgical Volume to Mortality: An Instrumental Variable Analysis. *Med Care* 2015; 53(12):1033-1039.
58. Greenland S. For and Against Methodologies: Some Perspectives on Recent Causal and Statistical Inference Debates. *Eur J Epidemiol* 2017; 32(1):3-20.
59. Laborde-Casterot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. *J Clin Epidemiol* 2015; 68(10):1232-1240.

Chapter 7

Unmeasured confounding in observational studies of management of cerebellar intracranial hemorrhage

Van Essen TA, Menon DK, Lingsma HF.

JAMA. 2020 Feb 18;323(7):665-666.

To the Editor

In a propensity score–matched cohort of 578 patients from 4 observational cohort studies, Dr Kuramatsu and colleagues showed that evacuation of medium-sized intracerebellar hematomas (approximate volume, 20 cm3) was not associated with better functional outcome.[1] Assessing treatment effectiveness in observational data is challenging because treatment decisions are based on patient characteristics that also are typically predictive of outcome, causing confounding by indication. Although the authors addressed this potential bias with propensity scores, we would like to emphasize the possibility of residual confounding.

In their study, surgically treated patients were younger, had worse Glasgow Coma Scale scores at presentation, had larger hematomas, and more often had intraventricular hemorrhage. In matching patients with the same risk of undergoing a surgical evacuation (the propensity), the authors suggested that treatment groups with similar prognosis were created. However, while measured confounding seems to have been properly addressed, unmeasured confounding may still be a problem. Many factors may influence decision-making in these patients, including frailty and preexisting conditions that could be contraindications for surgery. Contexts with strong measured confounding are also likely to show substantial unmeasured confounding. Propensity score matching is a statistically efficient alternative for regression-based covariate adjustment but still relies on the assumption that no unmeasured treatment preferences strongly relate to prognosis.[2,3]

A methodological study on comparable treatment considerations found that unmeasured confounding is not merely a theoretical problem.[3] In post hoc analyses of traumatic brain injury cohorts, analytical methods for surgery in traumatic intracranial hematomas and intracranial pressure–guided treatment were compared; propensity score matching was unable to account for unmeasured imbalances between treatment groups. A simulation study confirmed that propensity score matching resulted in an invalid estimate of the treatment effect in the case of unmeasured confounding,[3] which also was shown in other fields.[4]

Our view is that unmeasured confounding is an insurmountable problem in observational studies of acute neurosurgical decisions. A promising alternative for effect estimation is instrumental variable analysis. Although this method has its own difficulties, such as defining appropriate instruments and the necessity of large samples, it is not biased by unmeasured confounding.[3,5] Since the cohort in the study by Kuramatsu and colleagues came from 64 centers with likely differing practice culture among institutions, have the authors considered a regional comparison of treatment strategies?

REFERENCES

1. Kuramatsu JB, Biffi A, Gerner ST, et al. Association of surgical hematoma evacuation vs conservative treatment with functional outcome in patients with cerebellar intracerebral hemorrhage. *JAMA* 2019; 322(14):1392-1403.
2. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70(1):41-55.
3. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clin Epidemiol* 2018; 10:841-852.
4. Stukel TA, Fisher ES, Wennberg DE, et al. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; 297(3):278-285.
5. BrookhartMA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010; 19(6):537-554.

Chapter 8

Comparative effectiveness of surgery in traumatic acute subdural and intracerebral hematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe

Van Essen TA, Volovici V, Cnossen MC, Kolias A, Ceyisakar I, Nieboer D, Peppel LD, Heijenbrok-Kal M, Ribbers G, Menon D, Hutchinson P, Depreitere B, De Ruiter GCW, Lingsma HF, Steyerberg EW, Maas AI, Peul WC.

BMJ Open. 2019 Oct 16;9(10):e033513

ABSTRACT

Introduction

Controversy exists about the optimal treatment for patients with a traumatic acute subdural hematoma (ASDH) and an intracerebral hematoma/contusion (t-ICH). Treatment varies largely between different regions. The effect of this practice variation on patient outcome is unknown.

Here we present the protocol for a prospective multicentre observational study aimed at comparing the effectiveness of different treatment strategies in patients with ASDH and/or t-ICH. Specifically, the aims are to compare 1) an acute surgical approach to an expectant approach and 2) craniotomy to decompressive craniectomy when evacuating the hematoma.

Methods and analysis

Patients presenting to the emergency room with an ASDH and/or an t-ICH are eligible for inclusion. Standardized prospective data on patient and injury characteristics, treatment, and outcome will be collected on 1000 ASDH and 750 t-ICH patients in 60-70 centres within two multicentre prospective observational cohort studies: the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) and Neurotraumatology Quality Registry (Net-QuRe). The interventions of interest are acute surgery, defined as surgery directly after the first CT at presentation, versus late or no surgery, and craniotomy versus decompressive craniectomy. The primary outcome measure is the Glasgow Outcome Score – Extended at six months. Secondary outcome measures include in-hospital mortality, quality of life and neuropsychological tests. In the primary analysis, the effect of treatment preference (e.g. proportion of patients in which the intervention under study is preferred) per hospital will be analysed with random effects ordinal regression models, adjusted for case-mix and stratified by study. Such a hospital level approach reduces confounding by indication. Sensitivity analyses will include propensity score matching, with treatment defined on patient level. This study is designed to determine the best acute management strategy for ASDH and t-ICH by exploiting the existing between-hospital variability in surgical management.

Ethics and dissemination

Ethics approval was obtained in all participating countries. Results of surgical management of acute subdural hematoma and intracerebral hematoma/contusion will separately be submitted for publication in a peer-reviewed journal.

Trial registration

CENTER-TBI is registered within ClinicalTrials.gov with identifier NCT02210221 and Net-QuRe is registered with the Netherlands Trial Register NL 5761.

ARTICLE SUMMARY

Strengths and limitations of this study

- This comparative effectiveness study is a multicentre prospective observational cohort study that exploits variation in management strategies for intracranial hematomas to enable comparisons of the effectiveness of interventions.
- To overcome the bias by confounding the main analyses uses an instrumental variable approach; this approach is more robust to address unmeasured confounding than conventional individual patients level analysis methods
- Large sample sizes will be recruited: 1000 patients with acute subdural hematoma and 750 patients with intracerebral hematoma/contusion are expected, recruited in approximately 70 centres.
- Simulation studies confirmed the expected samples to be sufficient.
- The main limitation of this study is the absence of a randomised assignment of treatment strategy.

BACKGROUND

In Europe, over two million patients are admitted to hospital each year for traumatic brain injury (TBI), of whom 82.000 people die.[1] Survivors may have long-term physical, cognitive and mental disorders that often necessitate specialized care or rehabilitation programs. This debilitating morbidity has been estimated to lead to enormous societal costs.[2] An acute intracranial hematoma is the most frequently encountered pathological entity in TBI patients (Figure). Predominantly two specific subtypes, the acute subdural and an intracerebral hematoma or contusion (ASDH and t-ICH), occur in respectively 11 and 8% of all moderate TBI patients and up to 49% and 35% of all severe TBI patients [3-6]. Patients with an ASDH and/or t-ICH can show a wide array of symptoms, ranging from relatively mild complaints such as headache and nausea to severe conditions such as a comatose state (defined by a Glasgow Coma Scale (GCS) < 9).

Management of these traumatic hematomas can be challenging and requires the integration of clinical findings and diagnostic imaging. The main question is whether or not the patient needs to be immediately operated upon for evacuation of the hematoma and, secondly, if this surgical evacuation should be accompanied by a decompressive craniectomy (DC, i.e. leaving the bone flap out) or not.

Among comatose patients with a large ASDH, direct evacuation of the hematoma leads to a lower mortality.[3,4] Although questioning the effectiveness of surgery in these patients has been compared to questioning the effectiveness of a parachute in skydiving,[5,6] this cannot be generalized to most ASDH patients. Surgery may save a patient's life and preserve neurological function, some, however, may have an unsatisfactory functional outcome, ranging from severe neurological and cognitive deficits to a persistent vegetative state.[7-9] Furthermore, certain subgroups may not benefit from surgery because the damage by the primary injury is simply too devastating.[9] On the other hand, surgery may not always be necessary and a substantial proportion of patients managed conservatively have satisfactory outcomes.[10-14] In addition, timing of surgery plays a role, specifically for a t-ICH. Sometimes a t-ICH is initially managed conservatively, but may later be treated surgically when a patient deteriorates. The evacuation of the t-ICH can consist of removal of contused brain tissue. Finally, for the decision whether or not the evacuation of the hematoma should be accompanied by a DC, the surgeon weighs the increased complications rate of a DC against the risk of medically intractable diffuse brain swelling.[15]

High quality evidence for these decisions (*if, when* and *how)* is not available. For all guidelines that relate to TBI, the Brain Trauma Foundation (BTF) guideline for surgical management of intracranial hematomas, devised in 2005 by an international panel of experts, is based solely on class III evidence.[16,17] As a result these complex decisions are often based on intuition, regional training and experience of the

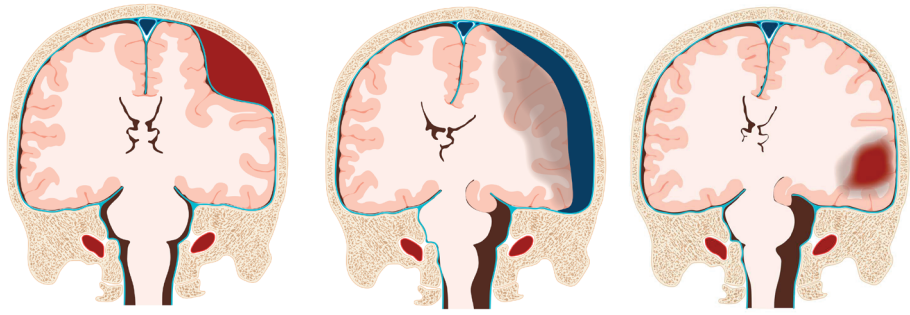


Figure. Different types of post-traumatic intracranial haematoma
(A) Epidural haematoma: a collection of blood between the skull and the outer membrane covering the brain (dura mater). (B) Subdural haematoma: a collection of blood located underneath the dura mater, generally associated with bruising of the underlying brain tissue (contusions). (C) Haemorrhagic contusion and intracerebral haematoma: lesions that reflect similar underlying pathologies, ranging from local bruising (contusions) to bleeding into the brain tissue (haematoma). Figure courtesy of Maartje Kunen, Medical Visuals, Arnhem, Netherlands. Reproduced with permission from.[24]

surgeon, leading to broad practice variation between centres, countries and even between surgeons within a centre.[5,18-22]

Therefore, a systematic evaluation in a (prospective) comparative study is proposed with comprehensive assessment of outcome, including perceived quality of life. We consider an observational comparative effectiveness design the next best alternative to a randomised controlled trial (RCT). These clinical questions are difficult to address in a randomised trial due to several methodological, ethical and pragmatic concerns.[23] Most importantly, the hesitance of clinicians to randomise surgical treatments because of strong opinions on the best treatment hampers realising a RCT.

Here, we present the design of a pragmatic prospective observational cohort study of surgical strategies for ASDH and t-ICH, conducted in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study and the Dutch embedded complete chain of care Neurotraumatology Quality Registry (Net-QuRe).[25,26]

OBJECTIVES

The primary aim is to compare the effectiveness of acute surgery with expectant management in the treatment of 1) ASDH and 2) t-ICH. The secondary goal is 3) to assess the effectiveness of craniotomy compared to DC for ASDH and/or t-ICH.

METHODS AND DESIGN

Design

This study uses a comparative effectiveness research (CER) design, a multicentre prospective observational cohort study that exploits variation in neurotrauma care to create and compare parallel study groups. The multicentre design is necessary to ensure the required number of patients with different neurotrauma treatment strategies for ASDH and t-ICH. The study is conducted in neurosurgical trauma centres in Europe that participate in CENTER-TBI.[25] CENTER-TBI collects data of patients with clinical diagnosis of TBI and an indication for a CT scan.[27] Data for the cohort described in this protocol will partly be collected through CENTER-TBI. The Dutch centres not participating in CENTER-TBI will acquire data through Net-QuRe, in a separate database with a similar data collection protocol.[26,28] The research question and methodology described here were designed before the inclusion of patients.

Patient and public involvement

Patients were involved in the priority of the research questions and selection of outcome measures in a 'patient advisory panel' consisting of patients and their caregivers. Furthermore, some patients and their caregivers have been asked to join a focus group on the feasibility of the follow-up (burden of the follow-up, the design/length of the questionnaires) and to advice on other research questions. The patient panel and their caregivers will be informed about the developments of the study and will be invited to participate in research meetings and discussions. Also, patients and family are informed of the study results through dedicated websites (Center-tbi.eu and Net-QuRe.nl).

A public debate is going on in the Netherlands about whether or not patients are treated too much at an older age or end-of-life stage. This debate has led to the start of formal campaign 'Choosing Wisely' of which the senior author WPE is organizing member.[29] The appropriateness of surgical TBI treatment has been prioritized.

Eligible study patients

The patients are selected from the observational cohorts from CENTER-TBI or Net-QuRe. Patients presenting to the emergency room with a clinical and radiological diagnosis of ASDH and/or a t-ICH are eligible for inclusion.

The in- and exclusion criteria are as following.

Inclusion criteria:

- ASDH and/or a large (>10 cc) t-ICH on a CT-scan
- Acute presentation (< 24 hours of injury) with history of head trauma

- Clinical indication for admission (ward or ICU)

Exclusion criteria:

- An ASDH or t-ICH due to penetrating injury, a spontaneous or iatrogenic ASDH/t-ICH
- Severe pre-existing neurological disorder that would confound outcome assessments

Patients are not excluded based on other clinical and radiological characteristics (such as: advanced age, antiplatelet/anticoagulant use, small hematoma volume). Radiological criteria for an ASDH or t-ICH/contusion are a high-density lesion, with or without radiological signs of raised intracranial pressure (ICP) and with or without mass effect (i.e. midline shift, compression of ventricles and/or basal systems). The minimal size of the t-ICH needs to be 10cc to be included.

Intervention procedures

Inherent to the observational design of this study the management strategies under investigation proceed according to local emergency- and intensive care protocols or surgeon's expertise. Consequently, the resulting variation in management is accepted and analysed. To gain insight into this variation detailed information is collected on the reasons for specific interventions or management strategies (see section 'why' questions).

Surgical strategy

Surgical treatment consists of evacuation of the hematoma and/or contusion with a craniotomy, or with a DC, defined as hematoma evacuation plus leaving a large portion of the skull open to allow brain swelling in the secondary phase, preventing subsequent brain injury. Generally, in Europe a craniotomy is performed for hematoma evacuation and DC when (intractable) swelling is seen intraoperatively or when swelling is expected (preventive). The decision for a DC can be made primarily, or secondarily by increasing the defect of the bone flap that is formed during a normal craniotomy. In conjunction to these surgical procedures the neurosurgeon will decide to place an intracranial pressure (ICP) monitor or not. The ICP device can be an intraparenchymal sensor or an external ventricular drain with a transducer for the ICP. The latter has an option to drain cerebrospinal fluid (CSF) and thereby lower ICP.

The operation will be performed by a qualified neurosurgeon or neurosurgical resident. The techniques for evacuating such hematomas are well established, although specific components of the operations may differ between surgeons. Our aim will be to collect pertinent operative data on a standardized data collection form.

The postoperative care on the ward or intensive care unit (ICU) generally is protocolized in European centres. The length of hospital stay will differ considerably between patients, ranging from one day to several months, mainly related to the severity of the injury. The aim for a patient is to be discharged as soon as possible. Furthermore, the supportive care is provided as described in the section 'expectant management'.

Expectant management, with possibly delayed surgery

For patients admitted to the ward, monitoring is in general by clinical neurological control (GCS and motor strength) with or without CT brain follow-up, whereas for those patients admitted to the ICU (mostly severe TBI) the diagnostic and therapeutic options include ICP monitoring with medical management of intracranial hypertension (i.e. hyperosmolar therapies, hyperventilation etc) and cerebral perfusion pressure (CPP).

Follow-up CT scans, performed during hospitalization, are collected and analysed centrally, independent from the treating physicians. Hereby, an estimation is made about the proportion of the evacuated hematoma and the change in density of lesions. Patients will be allocated to one of the treatment arms based on the initial treatment strategy. The data collection includes questions after each CT that ask whether or not the patient is transferred to the OR for an operative procedure. In doing so, the treatment 'arms' in this study can be carefully controlled based on the first CT on presentation (showing an ASDH and/or a t-ICH). The initial treatment regimen chosen will be one of either treatment arms, analysed according to an intention-to-treat approach.

Data collection

Data of care management by hospital personnel are registered in all departments. Data collection is done in a standardized electronic database, based on the 'common data elements' for TBI and web-based data collection protocol.[30,31]

Practice variation and provider profiling

Parallel to a survey on regional practice variation towards ASDH management in the Netherlands, we have performed provider profiling of neurosurgical care for TBI in Europe.[32] This study provides an exploration of the organization of neurosurgical care and treatment policy of TBI in all study centres. Such centre characterization allows specification of the local policy and standardized protocol. Structures and processes of care to be studied are patient volume, location of first ER evaluation, level of the trauma centre, referral policy, number of neurosurgeons, type of ICU and 24/7 CT availability. In addition, with regard to post-acute care, routine follow-up for

ER patients, ICU approaches to fluid load, hyperventilation, hyperosmolar therapy, timing of intracranial surgery, timing of extracranial surgery, glucose management, cerebral spinal fluid (CSF) drainage, DC, CPP management, coagulopathy treatment and ICP monitoring (parenchymal or CSF catheter). Whether or not consensus for divergent clinical decisions is agreed upon and whether or not hospital protocols are available and applied.

Admission data

In short, the 'common data elements' entail the collection of patient characteristics including demographics, comorbidities, associated extracranial injuries, neurological condition, prehospital information, hypoxic and hypotensive periods, and CT abnormalities. For the purpose of CER detailed information on processes of care will be collected within CENTER-TBI and Net-QuRe, including timing (of first CT, second CT, operation), surgery parameters, pre-hospital management and IC therapies (including ICP: pharmacological and/or DC). These data are collected on patient level, but also on hospital level (see previous paragraph).

'Why' questions

The observational design poses a challenge for inferring that the surgery caused the outcome instead of other factors. Several known and measured confounders (pupillary abnormalities, GCS and hematoma characteristics on CT) can be accounted for. However, for the decision to operate or not in intracranial hematoma, neurosurgeons select certain clinical, radiological and subjective 'gut feeling' characteristics that would normally go unmeasured. Therefore, the following efforts are undertaken to collect variables that normally will go unmeasured. To assess the effectiveness of different treatments for ASDH and t-ICH additional data are collected on an individual (doctor) level; the neurosurgeon, ICU physician and/or neurologist is asked to give their indication/reason to choose for surgery or conservative management (e.g. hematoma size, mass effect, clinical symptoms, clinical deterioration and/or other motivation), his or her motivation for the chosen procedure (DC or craniotomy) and the anticipated prognosis of the patient.

The motivation for surgery and the prognosis is collected before the decision for surgery or conservative management because afterwards the motivation could have been changed due to several factors such as intraoperative findings and the clinical course of the patient after the surgery.

Because of the infrastructure in TBI care, in which the clinician on-call is often outside the hospital and - in case of the neurosurgeon - will start with the surgery right after arrival in the hospital, the neurological and neurosurgical residents will assess their supervising clinician's motivation before the decision is carried out. To

control this process, the date and time of collecting these variables is collected as well.

Outcome measurements and endpoints

Within CENTER-TBI and Net-QuRe the outcome measures are assessed by face-to-face interviews, postal or emailed questionnaires or by telephone interviews at 3, 6 and 12 months after injury. Outcome assessment is done naïve for the research questions.

The primary endpoint is the 6-month Glasgow Outcome Score - Extended (GOSE[33]). The Glasgow Outcome Scale Extended (GOSE) is the most commonly used outcome measure in TBI. The GOSE grades disability on an 8-point scale incorporating physical deficits as well as emotional and cognitive disturbances affecting disability.[34,35] The GOSE is designed as a structured interview and can be applied through telephone[36] and the mail.[37]

Secondary endpoints are mortality, structural hematoma changes on CT, frequency and type of neurosurgical interventions, ICU and hospital length of stay (days), complications (hydrocephalus, intracranial haemorrhage, infection, pulmonary embolism, deep vein thrombosis and death), 'treatment failure' during the initial hospital admittance (patient in the expectant group who are operated at a delayed moment or patients in the early surgery group who are operated again), discharge to home (from the hospital, rehabilitation facility or nursing home), quality of life 6 and 12 months postinjury with the SF-12, the brain injury specific Quality of Life after Brain Injury questionnaire (Qolibri)[38] and cognitive tests. Details of these and other outcome measures are provided in our previous publication.[25]

Data analysis

Patient characteristics, hospital characteristics, and variation in both treatment and outcome variation will be described using descriptive statistics. To assess differences between groups, appropriate tests will be employed according to distribution and scale of measurement (Student's t-tests or Mann-Whitney U tests for continuous variables and Chi-squared tests, or Fisher's exact test for categorical variables). To examine effectiveness of interventions, proportional odds logistic regression models with the 8-point ordinal GOSE as outcome variable will be used. A proportional odds model increases statistical power in comparison to a conventional logistic regression model with a binary outcome.[39] The odds ratios derived from a proportional odds regression model could be interpreted as the odds ratio (OR) for shifting over the GOSE.[39]

The main challenge in the analyses is how to estimate a treatment effect in these observational data with strong confounding. Conventional methods, patient-level

analyses with covariate adjustment in regression modelling and propensity score matching, can insufficiently account for the (unmeasured) confounding in TBI.[40] Therefore, the main analyses will use the between-hospital variation in treatment for determining effectiveness by comparing regional treatment strategies. This is an instrumental variable (IV) approach. The instrument is the proportion of patients exposed to the intervention per hospital, determined as the proportion initially operated ASDH of total ASDH patients, initially operated t-ICH of total t-ICH patients and proportion of total ASDH or t-ICH patients exposed to primary DC (that forms a proxy for 'aggressiveness' of the neurosurgical staff). Total ASDH and ICH numbers are available through the registry. The instrument is entered as an independent variable to the analyses. The unmeasured and measured confounding at the hospital level, for example hospitals that perform more surgery also more often perform other treatments, is overcome with a multilevel analysis model.[41] In this model the random intercept should capture the measured and unmeasured confounders at hospital level, resulting in unbiased treatment effect estimates. The random intercept for each hospital represents the unexplained hospital effect (beyond all factors included in the model, including the instrument treatment preference). Assumptions of the IV approach will be checked according to our previous published case study.[40]

For these analyses, hospitals contributing at least 15 patients to the study sample are included to minimize the influence of chance. To increase statistical power, adjustment for potential patient level confounding will be made by adding the strongest predictors of outcome (age, GCS, pupillary response, CT characteristics (hematoma thickness and volume, subarachnoid haemorrhage, basal cistern compromise, other focal or diffuse lesions), hypoxic or hypotensive episodes and extracranial injuries) as covariates.[42] These factors were determined by prognostic modelling in the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) study based on a dataset of ten RCTs and three observational studies.[43] Thus, the treatment effect parameter will be the estimate for the effect of 'aggressiveness' on outcome from a random effects ordinal regression model with hospital as a random intercept.

In sensitivity analyses the instrument validity will be further explored by quantifying a priori collected data, the results of our survey[18] and the provider profiling of CENTER-TBI,[19] and comparing these to the post-hoc derived relative proportion exposed to the intervention per hospital.

In the secondary analyses, conventional regression modelling with covariate adjustment and propensity score matching is performed. In both these analyses actual treatment will be a binary treatment variable and GOSE as ordinal outcome variable. For ASDH surgery effectiveness, confounding will be controlled for by adding age,

GCS, pupil reactivity, hematoma thickness and midline shift as covariates in the model. For t-ICH effectiveness, confounding adjustment for age, GCS, hematoma volume, pupil reactivity, hematoma laterality and midline shift. For DC effectiveness, by age, GCS, pupil reactivity, midline shift and hematoma size (ASDH: thickness; t-ICH: volume).

Importantly, the effect of surgery is probably not uniform, as is suggested by empirical evidence[44,45] and by clinical experience. Therefore, effect modification by the following variables will be tested using interaction terms: GCS of ≥ 9, hematoma size >10 mm in diameter, midline shift >5 mm, time to treatment and baseline prognostic risk.[42]

Sample size

In CENTER-TBI and Net-QuRe together approximately 1000 patients with ASDH are expected. For t-ICH, 750 patients are expected. Parallel to the core study, 3500 and 3000 ASDH and ICH patients are expected in the registry respectively. These patients are recruited in approximately 70 centres.

Standard sample size calculations for these specific analyses are not readily available. Therefore, a simulation study was performed to calculate statistical power. The assumptions for these calculations were the following: 30, 50 or 70 hospitals, variation of intracranial operation among hospitals 10 to 90% and an effect estimate of OR 0.6 on unfavourable outcome. In addition, we assumed covariate adjustment and the ordinal analysis to increase power with 40 to 49%.[39] The simulation confirmed these sample sizes to be sufficient to obtain a power of 80% to detect a difference (assuming a 2-sided significance 0.05).

This is in line with preparatory simulation study we performed in which a true treatment effect was simulated specifically to assess the TBI specific associations between covariates and outcome.[40] This simulation study was built around the International and North American Tirilazad trial dataset (86 hospitals between 1992 and 1994) of the IMPACT dataset,[43] which was inflated to CENTER-TBI/ Net-QuRe numbers (respectively 750 and 1000 patients from 70 hospitals). We simulated a hypothetical intervention with an OR 1.5. For the association between the hypothetical intervention and confounders, we used the observed associations between intracranial operation and confounders in the Tirilazad dataset. We used six-month binary (functional) outcome as dependent variable, which was generated based on a combination of the prognostic effect of the confounders and the effect of the hypothetical intervention.

For analyses and simulations R statistical software with add-ons (the *rms* and *lme4* packages) is used.

Missing data

Missing baseline data will be imputed with multiple imputation (n=5).

Reporting

Reporting of our study will follow the STROBE statement with a special focus on instrumental variable analyses recommendations.[46]

Study limitations

The main limitation of this study is the absence of a randomised assignment of treatment or strategy. Risks of confounding by indication are reduced by instrumental variable analysis. The success of the primary analysis however, depends on the strength of the instrument, i.e. the difference in aggressive versus conservative practice style between physicians during the study period. The results of the provider profiling (before the study) are encouraging. As secondary analyses we perform more conventional approaches to adjust for confounding by indication (multivariable adjustment and propensity scores). The results of analytical approaches will be interpreted in the light of the assumptions they require and to what extent these are likely to be fulfilled in the data. The final conclusion will be drawn based on the joint results of all analyses.

DISCUSSION

There is controversy with regard to the initial neurosurgical management of ASDH and t-ICH. First, neurosurgeons are faced with an acute decision to operate or not, and second, are confronted by the choice to evacuate the hematoma with or without a DC. The complexity lies in the balance between too liberal surgical indications with an increased number of survivors with severe disabilities against inappropriate conservative management with unnecessary death and disability. In combination with the circumstances, i.e. urgency and time pressure as well as absence of peer consultation, these treatment decisions have been shown to lead to variation in surgical treatment between surgeons.

The proposed study will provide a strong level of evidence for surgical management of ASDH and t-ICH. We expect that the large natural existing practice variation in management of these intracranial lesions[18,19] could in part explain the unexplained between-centre variability in outcome in TBI.[47] Thereby, the impact on patients will probably be significant. Recognizing and implementing the most effective clinical treatment strategy could be an important step towards reducing the widely differing injury mortality rates across Europe.[48]

Current and ongoing studies are sparse. Since the BTF guideline, which was based on merely retrospective studies with small or selected study populations that were performed more than 10 years before the guideline,[5,10,11,49] there have been only some comparative studies. In our own retrospective analyses, early ASDH evacuation might be associated with lower odds of mortality and unfavourable outcome (GOS $\leqq$ 3).[44] This is the first report showing an effect estimate of surgery for ASDH. The clinical effectiveness of an early evacuation for t-ICH was challenged in the Surgical Trial in Traumatic Intracerebral Haemorrhage (STITCH-Trauma), an international multicentre pragmatic randomised controlled trial.[50] The study started in October 2009 but was halted due to a disbalance in recruited patients per country. In the analysis of the included patients, a strong (but non-significant) tendency towards benefit of early surgery was found on the primary endpoint the dichotomous GOS and there were significantly more deaths in the initial conservative treatment group. The effectiveness of a primary DC in patients with ASDH is currently being assessed in the recruiting RESCUE-ASDH randomised trial.[15]

Thus, these traumatic hematomas confront the neurosurgeon with a challenging surgical decision-making task, which, most likely due to a lack of general evidence, leads to broad variation in current surgical practice patterns. While RCTs can be delivered and provide high level evidence, they are challenging to conduct, hence the rationale for other methodological intervention paradigms. The high-quality observational study presented in this article, with a focus on the analysis of the differences in management and outcome, is expected to provide the much-needed further evidence in the field of surgical management of traumatic focal lesions.

ABBREVIATIONS

ASDH: acute subdural hematoma,
CENTER-TBI: Collaborative European NeuroTrauma Effectiveness research in TBI
CER: comparative effectiveness research,
CPP: cerebral perfusion pressure,
CSF: cerebrospinal fluid,
CT: computed tomography,
ER: emergency room,
GCS: Glasgow Coma Score,
GOSE: Glasgow Outcome Scale Extended,
ICU: intensive care unit,
ICP: intracranial pressure,
IMPACT: International Mission for Prognosis and Analysis of Clinical Trials in TBI,
IV: instrumental variable,

Net-QuRe: Neurotraumatology Quality Registry,
OR: operating room,
Qolibri: Quality of Live in Brain Injury,
RCT: randomised clinical trial,
TBI: traumatic brain injury,
t-ICH: intracerebral hematoma/contusion.

DECLARATIONS

Ethics and dissemination

Ethical approval for the studies CENTER-TBI and Net-QuRe has been received from each participating centre in the study before recruitment started. The list of sites, Ethical Committees, approval numbers and approval dates can be found on the website: https://www.center-tbi.eu/project/ethical-approval.
Written informed consent is obtained from the patient or the legal first representative on the ER and preferably as soon as possible. Center-TBI is registered at ClinicalTrials.gov (NCT02210221) and Net-QuRe is registered at the Netherlands Trial Register (NL 5761).[27,28]
Results of surgical management of ASDH and t-ICH will separately be submitted for publication in a peer-reviewed journal. The completion dates of CENTER-TBI and Net-QuRe are April 1st, 2020 and July 1st, 2022 respectively.
The data that support the findings of this study are available but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request, with permission of the CENTER-TBI and Net-QuRe management teams.

Competing interests

The authors declare that they have no competing interests.

Funding

The project described in this study protocol is funded by the *Hersenstichting Nederland* (the Dutch Brain Foundation, grant number ps2014.06) for Net-QuRe and the European Union seventh Framework Program (grant 602150) for CENTER-TBI. Additional support for CENTER-TBI was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA), from Integra LifeSciences Corporation (USA), and from NeuroTrauma Sciences (USA). The funding bodies had no role in the design of the study, collection, analysis, and interpretation of data and in writing

the manuscript. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Authors PH and AK are supported by the NIHR Global Health Research Group on Neurotrauma, which was commissioned by the National Institute for Health Research (NIHR) using UK aid from the UK Government (project 16/137/105). The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. PH is supported by a Research Professorship from the NIHR, the NIHR Cambridge Biomedical Research Centre, and the Royal College of Surgeons of England. AK is supported by the Royal College of Surgeons of England and a Clinical Lectureship, School of Clinical Medicine, University of Cambridge

Author contributions

TvE conceived of the study design, performed the statistical analysis and wrote the manuscript. GdR, VV, MC, LP, HL, BD, MH, GR, DM, PH, AK, ES, AM and WP participated in the design of the study and helped to draft the manuscript. DN, IC, HL and TvE performed the simulation studies. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

REFERENCES

1. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *The Lancet Public Health* 2016; 1(2):e76–e83.
2. Faul M, Wald MM, Rutland-Brown W, et al. Using a Cost-Benefit Analysis to Estimate Outcomes of a Clinical Treatment Guideline: Testing the Brain Trauma Foundation Guidelines for the Treatment of Severe Traumatic Brain Injury. *The Journal of Trauma: Injury, Infection, and Critical Care* 2007; 63(6):1271–8.
3. Seelig JM, Becker DP, Miller JD, Greenberg RP, Ward JD, Choi SC. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304(25):1511–8.
4. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; 58(3 Suppl):S16–24–discussionSi–iv.
5. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–92.
6. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003; 327(7429):1459–61.
7. Tallon JM, Ackroyd-Stolarz S, Karim SA, Clarke DB. The epidemiology of surgically treated acute subdural and epidural hematomas in patients with head injuries: a population-based study. *Can J Surg* 2008;51(5):339–45.
8. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012; 154(9):1555–61.
9. Nijboer JMM, van der Naalt J, Duis ten H-J. Patients beyond salvation? Various categories of trauma patients with a minimal Glasgow Coma Score. *Injury* 2010; 41(1):52–7.
10. Dent DL, Croce MA, Menke PG, et al. Prognostic factors after acute subdural hematoma. *The Journal of Trauma: Injury, Infection, and Critical Care* 1995;39(1):36–42–discussion42–3.
11. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993;121(3-4):100–8.
12. Bus S, Verbaan D, Kerklaan BJ, et al. Do older patients with acute or subacute subdural hematoma benefit from surgery? *Br J Neurosurg* 2019;33(1):51–7.
13. Gernsback JE, Kolcun JPG, Richardson AM, Jagid JR. Patientem Fortuna Adiuvat: The Delayed Treatment of Surgical Acute Subdural Hematomas-A Case Series. *World Neurosurg* 2018;120:e414–20.
14. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998;44(5):868–73.
15. Kolias AG, Viaroli E, Rubiano AM, et al. The Current Status of Decompressive Craniectomy in Traumatic Brain Injury. *Current Trauma Reports* 2018; 1–7.
16. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006;58(3 Suppl):S16–24–discussionSi–iv.
17. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006;58(3 Suppl):S25–46–discussionSi–iv.
18. Van Essen TA, De Ruiter GCW, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *Journal of Neurotrauma* 2017;34(4):881–9.
19. Van Essen TA, Den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. 2019;161(3):435-449.
20. Kolias AG, Scotton WJ, Belli A, et al. Surgical management of acute subdural haematomas: current practice patterns in the United Kingdom and the Republic of Ireland. *Br J Neurosurg* 2013;27(3):330–3.
21. Ghajar J, Hariri RJ, Narayan RK, Iacono LA, Firlik K, Patterson RH. Survey of critical care management of comatose, head-injured patients in the United States. *Crit Care Med* 1995;23(3):560–7.
22. Murray GD, Teasdale GM, Braakman R, et al. The European Brain Injury Consortium survey of head injuries. *Acta Neurochir* 1999;141(3):223–36.
23. Stein SC. Comparative effectiveness in neurosurgery: what it means, how it is measured, and why it matters. *Neurosurgical FOCUS* 2012;33(1):E1.

24. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12):987–1048.
25. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76(1):67–80.
26. The 3rd Joint Symposium of the International and National Neurotrauma Societies and AANS/CNS Section on Neurotrauma and Critical Care August 11–16, 2018 Toronto, Canada. *Journal of Neurotrauma* 2018; 35(16):A–1–A–285.
27. Maas AIR. CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI. *Clinicaltrials.gov* 2014;
28. Nederlands Trial Register [Internet]. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.
29. Choosing Wisely Netherlands Campaign. https://www.demedischspecialist.nl/onderwerp/campagne-verstandig-kiezen.
30. Maas AIR, Harrison-Felix CL, Menon D, et al. Standardizing data collection in traumatic brain injury. *Journal of Neurotrauma* 2011; 28(2):177–87.
31. Maas AI, Harrison-Felix CL, Menon D, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on demographics and clinical assessment. *Arch Phys Med Rehabil* 2010; 91(11):1641–9.
32. Van Essen TA, Den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir* 2019; 161(3):435-449.
33. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *Journal of Neurotrauma* 1998; 15(8):573–85.
34. Shukla D, Devi BI, Agrawal A. Outcome measures for traumatic brain injury. *Clin Neurol Neurosurg* 2011; 113(6):435–41.
35. Bullock MR, Merchant RE, Choi SC, et al. Outcome measures for clinical trials in neurotrauma. *Neurosurgical FOCUS* 2002; 13(1):ECP1.
36. Pettigrew LEL, Wilson JTL, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews. *Journal of Head Trauma Rehabilitation* 2003;18(3):252–8.
37. Wilson JTL, Edwards P, Fiddes H, et al. Reliability of postal questionnaires for the Glasgow Outcome Scale. *Journal of Neurotrauma* 2002; 19(9):999–1005.
38. Von Steinbuechel N, Petersen C, Bullinger M. Assessment of health-related quality of life in persons after traumatic brain injury--development of the Qolibri, a specific measure. *Acta Neurochir Suppl* 2005; 93:43–9.
39. Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. *Critical Care* 2011; 15(3):R127.
40. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clinical Epidemiology* 2018; 10:841–52.
41. Li B, Lingsma HF, Steyerberg EW, Lesaffre E. Logistic random effects regression models: a comparison of statistical packages for binary and ordinal outcomes. *BMC Med Res Methodol* 2011; 11:77.
42. Hernandez AV, Steyerberg EW, Butcher I, et al. Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. Journal of Neurotrauma 2006;23(9):1295–303.
43. Lingsma H, Andriessen TMJC, Haitsema I, et al. Prognosis in moderate and severe traumatic brain injury: external validation of the IMPACT models and the role of extracranial injuries. *J Trauma Acute Care Surg* 2013; 74(2):639–46.
44. Van Essen TA, Dijkman M, Cnossen MC, et al. Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population. *Journal of Neurotrauma* 2019 1;36(7):1184-1191.
45. Gregson BA, Mitchell P, Mendelow AD. Surgical Decision Making in Brain Hemorrhage. *Stroke* 2019;50(5):1108–15.
46. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363–9.
47. Lingsma HF, Roozenbeek B, Li B, et al. Large Between-Center Differences in Outcome After Moderate and Severe Traumatic Brain Injury in the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) Study. *Neurosurgery* 2011;68(3):601–8.
48. Eurosafe. Injuries in the European Union: Summary of Injury Statistics for the Years 2008-2010. Amsterdam, The Netherlands:

European Association for Injury Prevention and Safety Promotion. Available at: http://ec.europa.eu/health/data_collection/docs/idb_report_2013_en.pdf. 2013.

49. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998; 44(5):868–73.

50. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with traumatic intracerebral haemorrhage [STITCH(Trauma)]: the first randomised trial. *Journal of Neurotrauma* 2015; 32(17):1312-1323.

PART IV

THE EFFECTIVENESS OF NEUROSURGICAL INTERVENTIONS IN ACUTE SUBDURAL HEMATOMA

Chapter 9

Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population

Van Essen TA, Dijkman MD, Cnossen MC, Moudrous W, Ardon H, Schoonman GG, Steyerberg EW, Peul WC, Lingsma HF, de Ruiter GCW.

J Neurotrauma. 2019 Apr 1;36(7):1184-1191.

Portions of this work were presented at the 12th Symposium of the International Neurotrauma Society, Capetown, South-Africa, February 1-4, 2016.

ABSTRACT

Uncertainty remains on the optimal initial management of patients with traumatic acute subdural hematoma, leading to regional variation in surgical policy. This can be exploited to compare the effect of various management strategies and determine best practices. This article reports such a comparative effectiveness analysis of a retrospective observational cohort of traumatic acute subdural hematoma patients in two geographically distinct neurosurgical departments chosen for their – a-priori defined – diverging treatment preferences. Region A favored a strategy focused on surgical hematoma evacuation, while region B employed a more conservative approach, performing primary surgery less often. Region was used as a proxy for preferred treatment strategy to compare outcomes between groups, adjusted for potential confounders using multivariable logistic regression with imputation of missing data. In total, 190 patients were included: 108 from region A and 82 from region B. There were 104 males (54.7%). Matching current epidemiological developments, the median age was relatively high at 68 years (IQR, 54-76). Baseline characteristics were comparable between regions. Primary evacuation was carried out in 84% of patients in region A and 65% in region B ($p<.01$). Mortality was lower in region A (37% vs. 45%, $p=.29$), as well as unfavorable outcome (53% vs. 62%, $p=.23$). The strategy favoring surgical evacuation was associated with significantly lower odds of mortality (OR: 0.43; 95% CI: 0.21 to 0.88) and unfavorable outcome (OR: 0.53; 95% CI: 0.27 to 1.02) 3-9 months post-injury. Therefore, in the aging population of patients with acute subdural hematoma a treatment strategy favoring emergency hematoma evacuation might be associated with lower odds of mortality and unfavorable outcome.

INTRODUCTION

In 1983, Gelpke and colleagues compared survival after severe traumatic brain injury (TBI) between two neurosurgical departments in the Netherlands. They concluded that of the 18% difference in survival rate between centers, 10.5% was accounted for by differences in baseline characteristics, and the remaining 7.5% could reflect differences in management strategies.[1] This study can be regarded as comparative effectiveness research (CER) *avant la lettre* in the field of TBI. CER aims to relate naturally occurring treatment variation to differences in patient-relevant outcomes, measured in day-to-day clinical settings and broad populations.[2] This is increasingly recognized as a powerful alternative to randomized controlled trials (RCTs).[3] Many surgical trials have been hampered by protracted recruitment periods[4,5] and financial constraints,[6] while providing limited benefit to clinical management.[5,7–9] Moreover, CER could be worthwhile because, partly due to current treatment guidelines featuring low class evidence, considerable between-center differences in the clinical management of TBI are seen.[10–16]

"To operate or not?" is a burning clinical question every surgeon frequently has to answer. In the case of traumatic acute subdural hematoma (ASDH), whether the patient will benefit from direct surgical evacuation of the hematoma remains a contested issue. Though prompt surgery has been associated with improved survival,[17–20] reported mortality rates remain high, ranging from 40 to 60% in surgically treated patients of all trauma severities.[21] Conversely, it has been suggested that certain patients with a poor prognosis may not be treated at all,[22,23] and patients with minimal symptomatology or comatose ASDH patient with a minimal hematoma without extracranial explanations for his/her coma can successfully be treated conservatively.[24–27] Conservative treatment comprises of observation, serial neurological examinations and sometimes placement of an intracranial pressure (ICP) monitor with non-operative/medical management of intracranial hypertension when appropriate.

Thus, the decision to operate or not poses a clinical challenge for the neurosurgeon and should preferably be aided by guidelines based on comparison of treatment regimes. However, RCTs have never been done and comparative observational cohort studies with balanced treatment groups are unavailable. The most widely used surgical guidelines published by the Brain Trauma Foundation are consequently made up of weak evidence.[21] Therefore clinical decision-making is presently influenced by neurosurgeons' individual preferences for, or familiarity with treatment of traumatic ASDH. As a result, management strategies vary considerably between neurosurgical departments, even between those within dedicated level 1 trauma centers with protocolled emergency medicine schemes.[10–12] Clearly, there is a need for comparative studies to elucidate the optimal treatment of traumatic

ASDH. Since randomized surgical trials are not practically feasible because of moral boundaries of treating physicians, the comparison of cohorts between homogenous regions managing ASDH in different ways may be the best available alternative to assess the effectiveness of surgical therapy.
The objective of this study was to compare mortality and functional outcome between an immediate surgical and a conservative, less surgery driven approach for the treatment of traumatic ASDH.

MATERIALS AND METHODS

This study was conducted and reported according to the criteria of the 'Strengthening the Reporting of Observational Based Studies' (STROBE) statement.[28]

The Dutch healthcare system and regional treatment variation

Healthcare in the Netherlands is uniformly accessible to all patients, with equal distribution of resources among hospitals. Neurosurgical care for patients with TBI is provided at 11 level 1 trauma centers, serving separate areas according to regional referral policies. Training and licensing is equal among these centers. However, neurosurgical practices differ across these centers, probably due to local surgical customs handed down over the years: a recent survey assessing whether neurosurgeons would perform an operation in various patients with ASDH showed considerable between-center variation among Dutch neurosurgeons' attitudes towards patients with traumatic ASDH.[12] Based on this questionnaire, the centers that showed the most divergent view on whether to operate acutely or not in cases reflecting the whole clinical TBI severity spectrum (90.0% vs 14.3% for moderate TBI, 90.0% and 42.9% for severe TBI) were chosen before the start of the current study. In both centers the same Brain Trauma Foundation guideline-based ICU protocol for (refractory) raised ICP is employed while the neurosurgical departments do not employ a surgical protocol (e.g. the Brain Trauma Foundation guideline).

Study design, setting and population

Two patient cohorts were retrospectively identified at two neurosurgical departments, in geographically separate regions. Neurosurgeons from region A treat TBI patients at two neurosurgically collaborating hospitals within level 1 trauma centers and advocate primary surgical treatment of ASDH (through hematoma evacuation with or without decompression). Neurosurgeons from region B operate in a single level 1 trauma center and opt for surgery less often, suggesting a more conservative approach.[12] Both regions serve a homogeneous population of about 2 million people. Regions A and B employed 16 and 18 neurosurgeons respectively.

Eligibility criteria

The Dutch registry system for hospital funding appoints diagnosis and treatment codes to all patients visiting a hospital. Using this system as a screening tool, we consecutively identified all patients treated by a neurosurgeon for TBI between 2008 and 2012 in both regions. Thereafter, the national trauma registry was checked for any missed inclusions.[29] A broad set of inclusion criteria was applied: patients were included if they had sustained head injury with direct presentation to the emergency room, were over 16 years of age, and showed a hyperdense, crescent shaped lesion – indicative of an ASDH – on the CT-scan. Exclusion criteria were penetrating injury, non-traumatic ASDH, ASDH secondary to an earlier procedure, and patients presenting with concomitant intracranial focal lesions (i.e. intracerebral hematoma or epidural hematoma) that required emergency surgery. Patients withheld from treatment due to severe comorbidity or because they were deemed unsalvageable, were also excluded on the premises the outcome would have been the same regardless of treatment.

Variables

Data from electronic patient files were gathered on demographics, medical history, use of anticoagulants or antiplatelet agents, injury related variables, radiological variables, treatment variables, complications and outcome variables.

Injury related variables included trauma mechanism, first emergency room Glasgow Coma Scale (GCS) score, focal neurological symptoms (paresis, aphasia or cranial nerve deficit), pupillary light reflex, clinical deterioration (i.e. a decrease of more than 1 point on the GCS, new abnormal pupillary light reflex, or new focal neurological symptoms, from the time of first assessment), presence of significant extra-cranial injury, and primary presentation to the study hospitals.

Radiological variables were assessed from the first CT-scan. They included clot thickness, midline shift, patency of the basal cisterns, presence of cranial fractures, and presence of concomitant intracranial hemorrhage (subarachnoid hemorrhage, epidural hematoma, contralateral subdural hematoma, intraventricular hemorrhage, or intracerebral hematoma/contusion). We also noted if a second preoperative CT-scan was made and whether it showed radiological deterioration (i.e. presence of new focal lesion or >5mm increase in hematoma thickness).

Therapy related variables included type of management (conservative or surgical), type of surgery (craniotomy, decompressive craniectomy (DC), or other), use of an ICP monitor, and any delayed surgical procedures performed after the initial treatment was received. The maximum diameter of the DC was measured from postoperative CT-scans. Patients were considered surgically treated when a report was made on the indication and the surgical procedure was started after the last CT made on the emergency room. Patients were considered conservatively managed when the

neurosurgeon on call reported not to operate after the CT. Patients that were primarily conservatively managed could require surgery later on, after secondary deterioration. All complications requiring medical attention during admission (e.g. antibiotic treatment for infection) were noted. Complications were defined as intracranial (e.g. seizure, hydrocephalus), cardiovascular (e.g. arrhythmia, ischemia), respiratory (e.g. respiratory insufficiency, hypoxia), metabolic (e.g. electrolyte disturbances, renal failure), infections (e.g. pneumonia, wound infection), or other.

Outcome measures were mortality at discharge and functional outcome according to the Glasgow Outcome Score (GOS). Functional outcome was judged from outpatient follow-up letters at 3-9 months post trauma, and dichotomized into favorable (GOS 4-5) or unfavorable (GOS 1-3).[30]

Two authors from region A collected all data. To ensure uniform and unbiased collection, both contributors independently gathered data according to a standardized collection sheet. In case of uncertainty, variables were coded after consensus was reached through discussion.

This study was approved by the ethics committees of the two participating hospitals.

Statistical analysis

The median and interquartile range (IQR) were calculated for continuous variables and frequencies were reported along with percentages for categorical variables. To test for differences in patient characteristics, treatments and outcomes between regions, we used Pearson's chi-square test for categorical, and the Mann-Whitney *U* test for continuous variables. In order to provide a summary baseline prognostic score for both regions, a multivariable logistic regression model, based on all available variables featured in the CRASH-CT head injury prognosis model (age, GCS score, pupil reactivity to light, major extracranial injury, midline shift >5mm, traumatic subarachnoid hemorrhage, and obliteration of the basal cisterns), was used to calculate predicted probabilities for mortality and unfavorable outcome.[31]

To assess the effect of treatment strategy on outcome, we used region as proxy for treatment strategy. That strategy correlates with more surgeries (and possibly other aspects, see discussion). Assuming regional variation was the only determinant of treatment strategy, the region in which patients were treated was used as grouping variable to compare outcomes. A multivariable logistic regression model was used to estimate the effect of treatment strategy on outcome, adjusted for the confounders age, GCS score, pupil reactivity and hematoma thickness. In addition, subgroup analysis restricted to patients with mild to moderate TBI (GCS 9 to 15) was done. The regression analyses were done using a multiple imputed dataset created with the automatic imputation method of the impute function of SPSS. Missing data were reported for all variables at baseline. Results were considered statistically significant if $p<.05$. All analyses were performed using IBM's SPSS version 23.

RESULTS

Participants and presentation

A total of 612 cases were screened (N, region A=294; N, region B=318) of which 195 cases met the eligibility criteria: 109 from region A and 86 from region B. Five cases were excluded due to severe comorbidity (N, region A=1), or were deemed unsalvageable (N, region B=4, figure 1).

The study population included 104 males (54.7%) and the median age was 68 years (IQR, 54-76). Regions did not differ significantly on age, sex, use of anticoagulants, injury mechanism, GCS score, occurrence of focal neurological symptoms, pupillary exam, or frequency of major extracranial injury (table 1). Region A received more primary referrals than region B (63% vs. 21%, p<.01). Patients in region B more often experienced clinical deterioration (34% vs. 51%, p<.01). Region A had larger median hematoma thickness (14mm vs. 10mm, p<.01), larger median midline shift (12mm vs. 9mm, p<.01), and less cranial fractures (28% vs. 44%, p<.03). The baseline CRASH-CT predicted risk of unfavorable outcome was similar: 56% in region A and 53% in region B (p=.18). Missing values per variable used in both univariable and multivariable regression analyses did not exceed 5.8% (table 1).

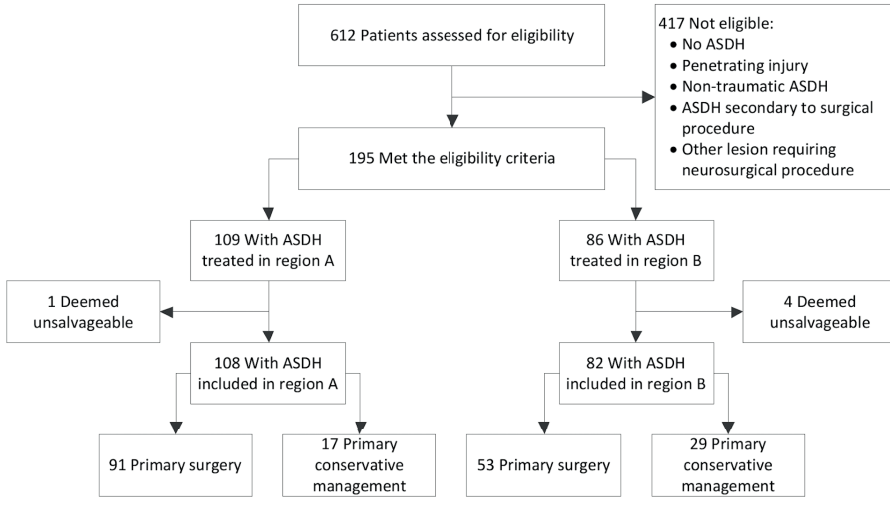


Figure 1. Patient inclusion flow chart showing the number of patients included in each region (region A: liberal surgical policy, region B: more conservative policy) and the definitive treatment received (either primary surgical or conservative).

Table 1. Clinical and radiological variables for the entire study population

Variable, % *missing*	Region A (N=108)	Region B (N=82)	p-value
Age, median (IQR), years, *0%*	70 (54 – 78)	65 (53 – 74)	.07
Male sex, No. (%), *0%*	57/108 (53%)	47/82 (57%)	.56
History of diabetes, No. (%), *1.6%*	14/105 (13%)	10/82 (12%)	1.00
Vascular history, No. (%), *1.6%*	60/105 (57%)	45/82 (55%)	.769
Anticoagulant, No. (%), *1.6%*			
Anticoagulants	34/107 (32%)	18/80 (23%)	.19
Platelet inhibitors	20/107 (20%)	16/80 (19%)	1.00
Mechanism of injury, No. (%), *2.5%*			
Fall	58/104 (56%)	45/81 (56%)	1.00
Assault	5/104 (5%)	1/81 (1%)	.23
Motor vehicle accident	12/104 (12%)	13/81 (16%)	.39
Fall from bike	12/104 (12%)	11/81 (14%)	.82
Other	17/104 (16%)	11/81 (14%)	.68
Primary presentation, No. (%), *0%*	67/106 (63%)	17/82 (21%)	<.01
Focal neurological symptoms, No. (%), *24.7%*	42/79 (53%)	28/64 (44%)	.31
Abnormal pupils, No. (%), *5.3%*			
One	13/101 (13%)	12/79 (15%)	.67
Two	14/101 (14%)	9/79 (12%)	.66
First GCS score, median (IQR), *2.6%*	9 (6 – 14)	12 (7 – 15)	.48
Initial motor (M) score, median (IQR), *29.5%*	6 (5 – 6)	5 (4 – 6)	.04
TBI severity, No. (%), *1.6%*			
Mild (GCS 13 to 15)	40/107 (37%)	29/80 (36%)	1.00
Moderate (GCS 9 to 12)	18/107 (17%)	20/80 (25%)	.20
Severe (GCS 3 to 8)	49/107 (46%)	31/80 (39%)	.37
Clinical deterioration, No. (%), *0%*	37/108 (34%)	44/82 (54%)	<.01
GCS score after deterioration, median (IQR), *5.2%*	8 (4 – 13)	8 (5 – 13)	.45
Major extracranial injury, No. (%), *3.2%*	12/102 (12%)	11/82 (13%)	.82
CT characteristics			
Thickness, median (IQR), mm, *5.8%*	14 (9 – 18)	10 (7 – 14)	<.01
Midline shift, median (IQR), mm, *4.2%*	12 (7 – 16)	8 (3 – 13)	<.01
Basal cisterns obliterated, No. (%), *4.2%*	39/101 (39%)	24/81 (30%)	.22
Concomitant SAH, No. (%), *2.1%*	24/104 (23%)	23/82 (28%)	.50
Concomitant contusion, No. (%), *2.6%*	20/104 (19%)	25/81 (31%)	.08
Concomitant EDH, No. (%), *2.1%*	7/104 (7%)	4/82 (5%)	.76
Concomitant SDH, No. (%), *2.1%*	8/104 (8%)	11/82 (13%)	.23
Concomitant IVH, No. (%), *2.1%*	2/104 (2%)	2/82 (2%)	1.00
Cranial fracture, No. (%), *2.1%*	30/106 (28%)	35/80 (44%)	.03
Second CT scan, No. (%), *1.6%*	23/105 (22%)	19/82 (23%)	.86
Radiologic deterioration, *2.4%*	14/22 (64%)[a]	10/19 (53%)[a]	.54
Predicted unfavorable outcome based on CRASH-CT variables (GOS ≤ 3, %), mean (IQR), *12.6%*	56% (42% – 75%)	53% (32% – 70%)	.18

Table 1. Clinical and radiological variables for the entire study population (*continued*)

Variable, % *missing*	Region A (N=108)	Region B (N=82)	p-value

[a] percentage of all second CT scans

IQR, interquartile range; No., Number; GCS, Glasgow Coma Scale; TBI, Traumatic Brain Injury; CT, Computer Tomography; SAH, subarachnoid hemorrhage; EDH, epidural hematoma; SDH, subdural hematoma; IVH, intraventricular hemorrhage; GOS, Glasgow Outcome Score

Interventions

Patients in region A more often received emergency surgery (84% vs. 65%, p<.01) or an ICP sensor (38% vs. 15%, p<.01). When undergoing surgery, patients were more likely to undergo DC in region B (32% vs. 55%, p<.01). The median size of DC in region B was somewhat larger (110mm vs. 116mm, p=.15). Both regions had a similar rate of delayed procedures (15% vs 16%, p=.57) and complications (table 2).

Table 2. Hospital course variables for the entire study population

Variable, % *missing*	Region A (N=108)	Region B (N=82)	p-values
ICP monitor placed, No. (%), *1.1%*	40/106 (38%)	12/82 (15%)	<.01
Emergency surgery, *0%*			
Total, No. (%)	*91/108 (84%)*	*53/82 (65%)*	<.01
Craniotomy, No. (%)	60/91 (66%)[a]	24/53 (45%)[a]	.02
DC, No. (%)	29/91 (32%)[a]	29/53 (55%)[a]	<.01
Other, No. (%)	2/91 (2%)[a]	0/53 (0%)[a]	.53
Size of DC, mdn (IQR)	110 (97 – 115)	116 (103.5 – 127)	.15
Delayed surgery, No. (%), *2.6%*			
Total	*16/103 (15%)*	*16/82 (19%)*	.57
Craniotomy	4/16 (25%)[a]	7/15 (44%)[a]	.46
DC	6/16 (38%)[a]	4/15 (25%)[a]	.70
Burrhole	4/16 (25%)[a]	3/15 (19%)[a]	1.00
Other	2/16 (13%)[a]	2/15 (13%)[a]	1.00
Complications, No. (%), *7.4%*			
Total	56/95 (59%)	50/81 (62%)	.76
Intracranial	30/95 (32%)	29/81 (36%)	.63
Cardiovascular	13/95 (14%)	17/81 (21%)	.23
Respiratory	4/95 (4%)	9/81 (11%)	.15
Metabolic	3/95 (3%)	9/81 (11%)	.07
Infection	30/95 (32%)	18/81 (22%)	.18
Other	1/100 (1%)	7/81 (9%)	.02

[a] Percentage within group of emergency or delayed procedures

ICP, intracranial pressure; mdn, median; No., Number; IQR, interquartile range; DC, decompressive craniectomy

Table 3. Output of logistic regression analyses. Numbers are odds ratios and 95% confidence intervals for the effect of treatment strategy on mortality and unfavorable outcome (Glasgow Outcome Score ≤ 3)

Analysis type	Mortality at discharge	Unfavorable outcome at 3-9 months
All patients		
Univariable (N=190), OR (95% CI)	0.75 (0.42 to 1.10)	0.74 (0.41 to 1.02)
Multivariable (N=190), OR (95% CI)[a]	0.43 (0.21 to 0.88)	0.53 (0.27 to 1.02)
Subgroup of mild-moderate TBI patients		
Univariable (N=110), OR (95% CI)	0.51 (0.22 to 1.18)	0.45 (0.21 to 0.96)
Multivariable (N=110), OR (95% CI)[b]	0.34 (0.13 to 0.91)	0.33 (0.14 to 0.77)

[a] controlling for age, GCS score, pupillary reactivity and hematoma thickness
[b] controlling for age, GCS score and hematoma thickness
OR, odds ratio; CI, confidence interval; TBI, traumatic brain injury; GCS, Glasgow coma scale

The effect of treatment strategy

Hospital mortality in region A was 37%, compared to 45% in region B (p=.29). Also, in region A 53% had an unfavorable outcome after 3-9 months, compared to 62% in region B (p=.23). Region showed a favorable effect of a more aggressive treatment strategy (region A) in both unadjusted (mortality OR, 0.75; 95% CI, 0.42 to 1.10; unfavorable outcome OR, 0.74; 95% CI, 0.41 to 1.02) and adjusted analysis (mortality OR, 0.43; 95% CI, 0.21 to 0.88; unfavorable outcome OR, 0.53; 95% CI, 0.27 to 1.02). Subgroup analysis restricted to patients with mild to moderate TBI (N=110) showed a similar effect for both mortality (adjusted OR, 0.34; 95% CI, 0.13 to 0.91) and unfavorable outcome (adjusted OR, 0.33; 95% CI 0.14 to 0.77) (table 3). A post-hoc analysis with adjustment for decompressive craniectomy and primary referral confirmed the main results (*supplementary tables 1 and 2*).

The effect of surgery on patient level

In multivariable analysis, surgery was associated with higher odds of in-hospital mortality (OR, 6.6; 95% CI, 1.43 to 30.8) and unfavorable outcome (OR, 1.56, 95% CI: 0.64 to 3.82, table 4).

Table 4. Output of logistic regression analyses. Numbers are odds ratio's and 95% confidence intervals for the effect of surgery on mortality and unfavorable outcome (Glasgow Outcome Score ≤ 3)

Analysis type	Mortality at discharge	Unfavorable outcome at 3-9 months
Effect of surgery on patient level		
Univariable, OR (95% CI)	9.7 (3.3 to 28.6)	3.5 (1.7 to 7.3)
Multivariable, OR (95% CI)[a]	6.6 (1.4 to 30.8)	1.6 (0.6 to 3.8)

[a] controlling for age, GCS score, pupillary reactivity and hematoma thickness

DISCUSSION

This study compared an aggressive surgical policy to a more conservative management strategy for traumatic ASDH. Though the study groups were comparable in terms of baseline prognosis, patients were significantly more likely to undergo emergency surgery in the expected region. A primarily surgically focused strategy was associated with a lower in-hospital mortality and unfavorable outcome.

Estimating causal treatment effects in non-randomized data is often impossible due to confounding by indication. Some of the baseline imbalance can be corrected through stratification or multivariable modeling (amongst other selection or analysis techniques). However, when we compared a surgical with a non-operative treatment on patient level in this study (table 4), in contrast to comparing treatment strategies on a center level, emergency surgery was associated with worse outcome even after adjusting for confounders. This suggests unmeasured confounding by indication, causing misleading effect estimates. The region-based comparison is a major strength of this study. It allowed for a 'natural experiment' where patients were 'allocated' to one of both policies based on where the accident occurred and not based on their baseline characteristics. This provided an opportunity for an analysis that likely has a considerable reduction of unmeasured confounding compared to an analysis comparing the actual treatment received. Based on the balance between groups with regard to measured confounders, we may speculate that there is also balance in unmeasured confounders. This assumption, however, cannot be statistically proven (as would neither be possible or rational in an RCT).

A weakness is that we compared surgical strategy in only two centers. It cannot be excluded that differences between regions in other aspects of care, e.g. other treatments or organization of care, caused the difference in outcome in addition to the surgical approach. To account for these differences in such a hospital-level approach more centers are generally needed to disentangle the care aspects that correlate with the treatment decision of interest. Therefore, we need to interpret our results with caution. The wide confidence interval of the effect estimates clearly underwrites this statement even more. A study with more hospitals is needed to allow adjustment for differences between the hospitals other than in the treatment of interest.

An obvious limitation in this context, although inherent to the observational nature, is that the region-based approach did not completely eliminate all differences in baseline confounders. Patients from region A presented directly to the study hospital more often (63% vs. 21%, $p<.01$). Primary presentation to a neurosurgical center improves patient outcome and has a close relationship with time to surgery,[32] both of which may have contributed to the lower rates of mortality and unfavorable outcome observed in region A. The higher incidence of clinical deterioration in region B may

be consequent to the larger number of secondary referrals. On the other hand, region B is characterized by relatively smaller hematoma thickness and midline shift (on the same time point CT), while having a higher proportion of accompanying contusions. However, the possible resulting confounding is adjusted for appropriately. Moreover, apparently the imbalances are evenly spread out because the cohorts of both regions have a similar prognosis in the validated CRASH model. So they were similar for the most important predictors of outcome on arrival to the study hospital.

Another limitation may be that the data collectors could not be blinded for hospital of admission, which might give rise to information bias. To minimize potential bias, a standardized and controlled data collection protocol was followed. Nevertheless, we need to consider that the GOS was estimated from clinic discharge and visit letters, instead of a structured interview.

Furthermore, this study needs an important note on generalizability. This is a relatively old population, with a high proportion of fall-related ASDH (56%). Recent comparable series of patients with ASDH of varying severities report mean ages of 55 to 58 years.[19,33,34] The high age in this study should come as no surprise considering the aging population in developed countries, but should be kept in mind when applying its results. Also, for a clinician to determine to which patients these results are relevant she/he needs to consider for what kind of ASDH patients the neurosurgery is consulted in the Netherlands. An unknown number of mild cases reviewed by the neurologist or neurology resident without consultation of a neurosurgeon were not included. This explains the relatively small number of conservatively treated patients (24% overall) in our cohort compared to recent studies, reporting 74-83% of ASDHs being treated nonoperatively.[33,34] And, though much less common, this also applies to very severe cases, not operated due to an extremely poor prognosis. Because the mild cases constitute the majority of TBI, and this patient category undoubtedly has an above-average prognosis, applying the favorable results of surgery to all ASDH patients would not be reasonable. While both the age and consultation patterns might influence the generalizability, we nonetheless consider our selection useful in research on surgical decision making, because our cohort is representative of the ASDH population currently presented to neurosurgeons.

The role of surgery for ASDH

Our results are in line with other recent studies reporting a positive effect of early/aggressive surgical management, mainly for severe TBI on mortality and functional outcome.[15,35] A recent report showed this could also be true for routine use of invasive ICP measurement for severe TBI.[14] On the other hand, when restricting to surgery, and the complete patient domain, i.e. ASDH patients with mild to severe TBI, previous studies have reported worse or similar outcomes in patients undergoing surgical

treatment.[24–26,32,36,37] However, all studies compared outcomes between surgically and non-operatively treated patients at the patient level rather than a regional level, potentially leading to confounding by indication, because more severely injured patients are more likely to be operated. As mentioned above, when performing a conventional analysis on our cohort, surgery was associated with increased mortality and unfavorable outcome in our data. Hence, the distorting effect of confounding by indication in TBI supports the use of a comparative effectiveness approach when an RCT is not feasible for whatever reason.

When discussing the role of surgery in TBI, the use of decompressive craniectomy cannot be left unmentioned. Region B used DC significantly more often, despite equal distribution of prognostic factors. This could reflect another variation in surgical strategy or be consequent to the higher number of secondary referrals, resulting in presentation at a later stage, when brain swelling has started to occur. There is limited evidence on the use of primary DC in the treatment of ASDH, and studies comparing craniotomy to DC are likely confounded by indication as well.[38–40] Consequently, the effect of more frequent use of DC in region B on our outcome measures is uncertain. The planned RESCUE-ASDH trial will use an experimental comparative effectiveness design to clarify the value of DC as a primary treatment in severe TBI.[11]

This study reports an example of the practice variation in surgical treatment of traumatic ASDH. Advantage can be taken of this variation for CER. Larger cohorts with more hospitals are required to perform robust analyses to explore the ability of this method to infer causality, and with enough statistical power to study specific substrata according to age and trauma severity. The availability of such cohorts, with prospectively gathered, trial quality data from real-world settings, will allow initiatives such as Net-QuRe and CENTER-TBI to answer urgent clinical questions to provide the much needed guidance for the treatment of TBI.[41]

CONCLUSION

In this comparative study of surgery for ASDH, an aggressive management strategy favoring emergency evacuation of the hematoma was associated with better outcome. This conclusion derives from a contemporary cohort of relatively old traumatic ASDH patients that reflects the current population presented to a neurosurgeon. Larger, prospective, comparative studies with more hospitals are needed to confirm this effect of surgery and to explore generalizability.

ACKNOWLEDGEMENTS

Funding/support

The European Union seventh Framework Program (grant 602150) for Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI). Hersenstichting Nederland (Dutch Brain Foundation, project PS2014-06) for Neurotraumatology Quality Registry (Net-QuRe). No industry affiliation.

Portions of this work were presented in an oral presentation as a plenary lecture at the 12th Symposium of the International Neurotrauma Society, Capetown, South Africa, February 1-4, 2016.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

Supplemental material available online: https://www.liebertpub.com/doi/suppl/10.1089/neu.2018.5869

Tables S1 and S2

REFERENCES

1. Gelpke GJ, Braakman R, Habbema, JD, Hilden J. Comparison of outcome in two series of patients with severe head injuries. *J Neurosurg* 1982; 59, 745–750.
2. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurg FOCUS* 2012 33, E3.
3. Maas AI, Menon DK, Lingsma HF, et al. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. *J Neurotrauma* 29, 32–46.
4. Hutchinson, P.J., Corteen, E., Czosnyka, M., et al. Decompressive craniectomy in traumatic brain injury: the randomized multicenter RESCUEicp study. *Acta Neurochir Suppl* 96, 17–20.
5. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012; 367, 2471–2481.
6. Gregson BA, Rowan EN, Francis R, et al. Surgical Trial In Traumatic intraCerebral Haemorrhage (STITCH): a randomised controlled trial of Early Surgery compared with Initial Conservative Treatment. *Heal. Technol Assess* 19, 1–138.
7. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; 364, 1493–1502.
8. Maas AIR, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. *Neurotherapeutics* 2010; 7, 115–126.
9. Tolias CM, Bullock MR. Critical appraisal of neuroprotection trials in head injury: what have we learned? *NeuroRx* 2004. 1, 71–79.
10. Kolias AG, Belli A, Li LM, Timofeev I, et al. Primary decompressive craniectomy for acute subdural haematomas: results of an international survey. *Acta Neurochir* 2012; 154, 1563–1565.
11. Kolias AG, Scotton WJ, Belli A, et al. Surgical management of acute subdural haematomas: current practice patterns in the United Kingdom and the Republic of Ireland. *Br J Neurosurg* 2013; 27, 330–333.
12. Van Essen TA, De Ruiter GCW, et al. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; 34, 881–889.
13. Dawes AJ, Sacks GD, Cryer HG, et al Compliance With Evidence-Based Guidelines and Interhospital Variation in Mortality for Patients With Severe Traumatic Brain Injury. *JAMA Surg* 2005; 150, 965–972.
14. Alali AS, Fowler RA, Mainprize TG., et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *J Neurotrauma* 2013; 30, 1737–1746.
15. Hartings JA, Vidgeon S, Strong AJ, et al. Surgical management of traumatic brain injury: a comparative-effectiveness study of 2 centers. *J Neurosurg* 2014; 120, 434–446.
16. Compagnone C, Murray GD, Teasdale, et al. The management of patients with intradural post-traumatic mass lesions: a multicenter survey of current approaches to surgical management in 729 patients coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 57, 1183–1192.
17. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma: major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304, 1511–1518.
18. Wilberger Jr. JE, Harris M, Diamond DL. Acute subdural hematoma: morbidity, mortality, and operative timing. *J Neurosurg* 1991 74, 212–218.
19. Leitgeb J, Mauritz W, Brazinova A, et al. (2012). Outcome after severe brain trauma due to acute subdural hematoma. *J Neurosurg* 2012; 117, 324–333.
20. Matsushima K, Inaba K, Siboni S, et al. Emergent operation for isolated severe traumatic brain injury: Does time matter? *J Trauma Acute Care Surg* 2015; 79, 838–842.
21. Bullock MR, Chesnut R, Ghajar J, et al. Surgical Management of Traumatic Brain Injury Surgical management of acute subdural hematomas. *Neurosurgery* 2006 58, S16–24; discussion Si–iv.
22. Scotter J, Hendrickson S, Marcus HJ, Wilson MH. Prognosis of patients with bilateral fixed dilated pupils secondary to traumatic extradural or subdural haematoma who undergo surgery: a systematic review and meta-analysis. *Emerg Med J* 2015; 32, 654–659.
23. Nijboer JMM, Van der Naalt J, Ten Duis HJ. Patients beyond salvation?. Various categories of trauma patients with a minimal Glasgow Coma Score. *Injury* 2010 41, 52–57.

24. Croce MA, Dent DL, Menke PG, et al. Acute subdural hematoma: nonsurgical management of selected patients. *J Trauma* 1994 36, 820–827.
25. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *J Trauma* 1998 44, 868–873.
26. Feliciano CE, De Jesus O. Conservative management outcomes of traumatic acute subdural hematomas. *P R Heal. Sci J* 2008 27, 220–223.
27. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993 121, 100–108.
28. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12, 1495–1499.
29. Goslings JC, Gouma DJ. [Trauma registration. A promising, but difficult process]. N*ed Tijdschr Geneeskd* 2009 153, 744–746.
30. Jennett B, Bond M. Assessment of outcome after severe brain damage. *The Lancet* 1975; 1, 480–484.
31. Perel P, Arango M, Clayton T, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 336, 425–429.
32. Stone JL, Lowe RJ, Jonasson O, et al. Acute subdural hematoma: direct admission to a trauma center yields improved results. *J Trauma* 1986 26, 445–450.
33. Bajsarowicz P, Prakash I, Lamoureux J, et al. Nonsurgical acute traumatic subdural hematoma: what is the risk? *J Neurosurg* 2015 123, 1–8.
34. Ryan CG, Thompson RE, Temkin NR, et al. Acute traumatic subdural hematoma: current mortality and functional outcomes in adult patients at a Level I trauma center. *J Trauma Acute Care Surg* 2012 73, 1348–1354.
35. Hedges JR, Newgard CD, Veum-Stone J, et al. Early neurosurgical procedures enhance survival in blunt head injury: propensity score analysis. *J Emerg Med* 2009 37, 115–123.
36. Dent DL, Croce MA, Menke PG, et al. Prognostic factors after acute subdural hematoma. *J Trauma* 1995 39, 33–36.
37. Tierney KJ, Nayak NV, Prestigiacomo CJ, Sifri ZC. Neurosurgical intervention in patients with mild traumatic brain injury and its effect on neurological outcomes. *J Neurosurg* 2015 124, 538–545.
38. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir* 2012 154, 1555–1561.
39. Chen SH., Chen Y, Fang WK, et al. Comparison of craniotomy and decompressive craniectomy in severely head-injured patients with acute subdural hematoma. *J Trauma* 2011; 71, 1632–1636.
40. Woertgen C, Rothoerl RD, Schebesch KM, Albert R. Comparison of craniotomy and craniectomy in patients with acute subdural haematoma. *J Clin Neurosci* 2006 13, 718–721.
41. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; 76, 67–80.

Chapter 10

Surgery versus conservative treatment for traumatic acute subdural hematoma: a prospective, multicentre, comparative effectiveness study

Van Essen TA, Lingsma HF, Dana Pisică, Singh RD, Volovici V, Den Boogert H, Younsi A, Peppel LD, Heijenbrok-Kal M, Ribbers G, Walchenbach R, Menon D, Hutchinson P, Depreitere B, Steyerberg EW, Maas AI, De Ruiter GCW, Peul WC, and the CENTER-TBI Investigators and Participants.

The Lancet Neurol. 2022 Jul;21(7):620-631.

Portions of this work were presented at the 15th Symposium of the International Neurotrauma Society, Berlin, Germany, July 17-20, 2022.

SUMMARY

Background

Despite being well-established, acute surgery in traumatic acute subdural hematoma (ASDH) is based on low-grade evidence. We aimed to compare the effectiveness of a strategy preferring acute surgical evacuation with one preferring (initial) conservative treatment in ASDH.

Methods

Using the observational, multicentre, European cohort CENTER-TBI, we conducted a prospective comparative effectiveness study among patients with ASDH, presenting within 24 hours after injury. In an instrumental variable analysis, we compared outcomes between centres according to treatment preference, measured by the case-mix adjusted proportion acute surgery per centre. The primary endpoint was functional outcome rated by the 6-months Glasgow Outcome Scale Extended, estimated with ordinal regression as a common odds ratio (OR), adjusted for prespecified confounders. Variation in centre preference was quantified with the median odds ratio (MOR).

Findings

We included 1407 patients with ASDH from 65 centres. Acute surgical evacuation was performed in 336 patients (24%), in 245 (73%) by craniotomy and in 91 (27%) by decompressive craniectomy. Delayed surgery after initial conservative treatment (n=982) occurred in 107 patients (11%). The proportion acute surgery ranged from 6 to 52% (IQR 12-36%) between centres with a twofold higher probability of receiving acute surgery for an identical patient in one versus another random centre (adjusted MOR for acute surgery 1·8 [$p < 0·0001$]). Centre preference for acute surgery over initial conservative treatment was not associated with better outcome (OR per 24% (IQR) more acute surgery in a centre 0·92 [95% CI 0·77-1·09]). This was consistent in the group of patients without unreactive pupils or a GCS of 15.

Interpretation

Similar patients with ASDH, without an extremely poor or good prognosis at presentation, were treated differently due to varying treatment preferences. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with better outcome. Therefore, in a patient with an ASDH for whom a clinician sees no clear superiority in acute surgery vs. conservative strategy, initial conservative treatment may be considered.

Funding
The *Hersenstichting Nederland* (the Dutch Brain Foundation), the European Commission seventh Framework Program, the Hannelore Kohl Stiftung (Germany), OneMind (USA), Integra LifeSciences Corporation (USA), and NeuroTrauma Sciences (USA).

Introduction

Acute subdural hematoma (ASDH) is the most prevalent focal lesion in traumatic brain injury (TBI) and is associated with high mortality and long-term neurocognitive morbidity.[1] One of the cornerstones of treatment is immediate neurosurgical management: acute hematoma evacuation or initial conservative treatment with potential delayed surgery.[2,3]

In patients with rapid neurological deterioration due to a large ASDH the decision to operate in the acute phase is clear: without acute surgery a high intracranial pressure (ICP) will persist and the patient will die. In most cases however, the benefit of acute surgery is less clear and patients may - at least initially - be safely managed conservatively. It requires balancing surgery with potential complications against initial conservative treatment with a risk of early death and disability due to irreversible deterioration.

Current Brain Trauma Foundation (BTF) guidelines advise acute surgery for ASDHs thicker than 10 mm or with midline shift greater than 5 mm, irrespective of clinical condition or patient characteristics,[4] but the strength of underpinning evidence is low, with only non-comparative studies in small, selected populations.[5-9] In the emergency setting, without high-level evidence, neurosurgeons are left with intuition and experience, formed by regional training and centre treatment culture, to guide their decision.

Consequently, the threshold for ASDH surgical evacuation varies substantially between centres.[10,11,12] Strong treatment preferences deeply rooted in centres seem to underlie this practice variation and reflect a lack of equipoise, a necessary premise for a randomised controlled trial (RCT).

Practice variation, however, provides opportunities to study the effectiveness of interventions in clinical reality by relating treatment variation to outcome.[13] Within the large observational cohort study 'Collaborative European NeuroTrauma Effectiveness Research in TBI' (CENTER-TBI), designed as comparative effectiveness study, preferred local treatment strategies were accepted and exploited to estimate their effectiveness in real-life practice.[14] Our aim was to compare the effectiveness of a strategy of acute surgical evacuation with one preferring initial conservative treatment in patients with ASDH.

METHODS

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology-statement with instrumental variable (IV) recommendations.[15,16] The research question, design, outcomes, analysis, subgroups and sample size calculations were defined before patient enrolment and have been published.[14] CENTER-TBI is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (RRID: SCR_015582). This study corresponds to Stage A in the IDEAL Framework.[17]

Study population

Patients with TBI, presenting within 24 hours after trauma, with a brain CT and without pre-existing severe neurological disorders were included in CENTER-TBI, from 2014 through 2017, in centres across Europe and Israel.[18,19] For this study, we selected patients with ASDH regardless of size and presumed necessity for surgical treatment. We excluded brain dead patients and those considered by the treating physician to be not salvageable due to injury deemed unsurvivable, in whom active treatment was not indicated. Due to the design of comparing treatment preferences, the study population inherently reflects the "real-life" clinical dilemma who to surgically treat acutely (appendix p 16). However, for interpretation purposes, we restricted the main analysis also to those "clinical equipoise" patients, being those without an extreme prognosis on either side of the spectrum. Specifically, patients with one or two unreactive pupils (poor prognosis) and patients with a GCS 15 (relatively good prognosis) were excluded for this main analysis.

CENTER-TBI was conducted in accordance to Good Clinical Practice (CPMP/ICH/135/95). Informed consent by patients or legal representatives was obtained according to local legislations.

Centre characteristics and data management

Centre characteristics were collected in prior performed surveys.[12,20] Questions included the centre's policy towards the threshold for acute surgery, which was used in sensitivity analyses (appendix pp 13-14). Other treatment decisions, such as prehospital care, possibly related to the surgical threshold can impact the internal validity of our study. We have therefore performed extensive cluster analysis, of which part is separately published.[21] The main conclusion was that treatment preferences within a centres are unrelated.

Data were collected by trained personnel using web-based case report forms (QuesGen Systems Incorporated, Burlingame, CA, USA), coded with the Common Data Elements scheme.[22] Complete CENTER-TBI methodology was published separately.[23]

Interventions

Acute surgery was defined as surgery directly after the first CT-scan, conservative treatment was defined as best medical management (after the first scan) with potential delayed surgery. Neurosurgeons were asked at each CT if and why surgery was indicated, checked by actual operating room transferal and by surgery codes/description. Surgical treatment was at the discretion of the treating neurosurgeon and consisted of ASDH evacuation by craniotomy or by additionally performing a (primary) decompressive craniectomy (DC), defined as craniotomy without bone flap replacement to allow for current or near-future brain swelling. If deemed necessary, surgery of concomitant skull or brain lesions was performed simultaneously. The initial conservative approach was defined as best medical management after the first scan, with clinical monitoring on the ward, medium-care- or (neurocritical) intensive care unit (ICU) and included possible ICP monitoring and delayed surgical evacuation).

Outcomes

The primary outcome was the Glasgow Outcome Scale Extended (GOSE), an 8-point scale ranging from 1 (death) to 8 (upper good recovery), at 6 months.[24] The use of the GOSE as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI group (IMPACT Common Data Elements). Secondary outcomes included in-hospital mortality, progression on CT/MRI, hospital length of stay (days), discharge destination, and 6-months quality of life assessed with the brain injury-specific Quality of Life after Brain Injury Questionnaire (Qolibri).[25] Outcome assessments were standardized and administered by interview or postal questionnaire.[18]

Statistical analysis

Baseline characteristics are presented using descriptive statistics and compared between treatment groups with standardized mean differences. Practice variation was described as the proportion (%, interquartile range [IQR]) of patients undergoing acute surgery per centre. To quantify and compare the between-centre differences in acute surgery, we calculated the median odds ratio (MOR). The MOR quantifies treatment variation between centres that is not attributable to chance and not explained by other (case-mix) factors.

The outcomes were analysed with respect to centre treatment strategy (and not actual treatment) in instrumental variable (IV) analyses.[26-28] Specifically, this was a comparison of centres with different preferences for acute surgical evacuation, quantified by the case-mix adjusted probability of performing acute surgery (as

opposed to initial conservative treatment) as observed per centre. To minimize the influence of chance, only centres with at least 15 patients were included. We presented baseline characteristics and the Corticosteroid Randomization after Significant Head Injury (CRASH)-CT-score, a validated baseline prognostic model,[29] across quartiles of the instrumental variable, i.e. the case-mix adjusted probability of performing acute surgery. The first category contains centres least likely to perform acute surgery, fourth quartile contains centres most likely to perform acute surgery. The IV analysis is based on preference for acute surgery rates as a continuous variable, the quartiles are presented to provide insight in the comparability of patient populations across the instrument, which allows the reader to evaluate how comparable the patient characteristics are (IV assumption: the instrument is independent of confounders).[16,30]

The primary effect estimate was the adjusted common OR for a shift in the direction of a better outcome on the GOSE (proportional odds). This ratio was estimated with random-effects ordinal regression with the instrument (adjusted probability of performing acute surgery) as a continuous treatment variable. Random-effect accounts for other between-centre differences than the factors included in the model. Confounding was further addressed by adjusting for the predefined variables age, GCS, pupil reactivity, ASDH size and midline shift.[14] The common OR is presented as a comparison between the first and the fourth quartile (IQR) of the instrument (the adjusted probabilities for undergoing acute surgery) and can be interpreted as the odds for a more favourable outcome when comparing centres favouring a strategy of acute surgery to those favouring initial conservative treatment.

The main analysis was post-hoc repeated on those patients for whom clinical equipoise exists, as would have been done for a RCT. In this post-hoc analysis, we excluded patients without an extremely good (i.e. GCS 15) or an extremely poor (one or two unreactive pupils) prognosis. While most clinicians would agree that there is more equipoise in these patients, and thus intuitively feel that the results might be applicable to them, we did not define this analysis in the protocol and thus label it post-hoc.

To assess the consistency of the (ordinal) estimate and the plausibility of proportionality of the OR, we present ORs for multiple cut-offs on the GOSE.

The association of surgical preferences with outcome was also estimated by linear regression with the fixed effect centre coefficients as independent variable and the (continuous) mean GOSE per centre as dependent variable. These results are graphically represented in scatter plots.

Secondary outcomes were analysed with random-effects logistic and linear regression.

The primary, centre-level, analysis, was supplemented with several sensitivity analyses including predefined subgroup analyses. Specifically, one of the sensitivity

analyses was an instrumental variable analysis using the surveyed centre's preference for the use of surgery, as captured through the prior performed provider profiling, as the instrumental variable. Additionally, we performed sensitivity and subgroup analyses on patient-level, with multivariable regression and propensity score matching. A consistency in estimates with the employed methods would strengthen our findings.[31] All sensitivity analyses were performed for the primary outcome.
The supplementary appendix provides additional methodological details for all analyses.
Power calculations showed that assuming inclusion of 1000 ASDH patients would provide 80% power to detect an OR of 0·6.[14]
Analyses were performed in R-software version 3.5.3 and RStudio version 1.1.463. Missing data were multiply imputed with the Multiple Imputation by Chained Equations (MICE) package (n=5), assuming to be missing at random.
Comparison of descriptive characteristics are presented with standardized mean differences (SMD) and p-values between compared groups. ORs and Beta's are presented with 95% confidence intervals (CIs) calculated by bootstrapping with 500 samples.

Role of the funding sources

The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

Patient characteristics

Of 4559 patients with TBI, 1407 patients with ASDH were included. Acute surgery was performed in 336 patients (25%), at a median of 3·8 (IQR 2·5 – 6·5) hours after injury (appendix pp 17-21). Eighty-nine cases had an extremely poor prognosis or were brain dead, resulting in 982 out of 1071 patients treated conservatively, of which 107 patients (11%) receiving delayed surgery (craniotomy or DC), at a median of 19·1 (IQR 8·1 – 84·6) hours after injury. Of the 336 patients acutely operated, 91 (27%) underwent a primary DC (Figure 1). Of the initial conservatively treated by medical management, 313 patients (32%) received ICP monitoring, 107 patients (11%) underwent delayed DC or craniotomy for an ASDH or ICH and 20 patients (2%) received a (delayed) burr hole drainage for a chronic subdural hematoma (appendix pp 17-21). After excluding patients from centres with fewer than 15 patients (n = 158),

1160 patients were included in the IV analysis, 292 patients with acute surgery and 868 with (initial) conservative treatment (Figure 1).
The acute surgery cohort had a lower GCS at presentation, larger ASDHs, and a greater proportion of accompanying large contusions compared to the conservative cohort (appendix pp 17-21). The main reason for acute surgery was 'emergency' (57%), while in mild/moderate TBI, 'mass effect on CT' was relatively more often the motivation for surgery compared to severe TBI (appendix pp 26-27). Ninety-two percent of patients with 1 nonreactive pupil and large hematoma received acute surgery.
The main reasons for not performing acute surgery were that the lesion was considered not to benefit from surgery (considered 'no surgical lesion') or had little mass effect. The main reasons for secondary surgery after initial conservative treatment were '(suspicion of) raised ICP', 'mass effect on CT' and 'clinical deterioration' (appendix pp 26-27). Ninety-three percent of patients with a GCS of 15 received conservative treatment (initially).
In 89 patients, neither treatment was performed because these patients were considered not salvageable due to injury deemed unsurvivable (appendix pp 26-27). These patients had severe clinical and radiological characteristics and an in-hospital mortality of 96% with a median time to death of 21 hours, preceded by a multidisciplinary treatment limiting decision in most patients (79%, appendix pp 22-25).

Practice variation

The proportion of patients undergoing acute surgery per centre ranged from 5·6 to 51·5% (IQR, 12·3-35·9%) between centres (appendix p 28). Practice variation was low for patients with a GCS of 15, in whom initial conservative treatment varied between 91 and 100%, and for patients with one nonreactive pupil and a large hematoma of whom 100% received acute surgery in 13 out of 16 centres.
The MOR for acute surgery was 1·8 ($p < 0·0001$), reflecting a nearly twofold higher probability of receiving acute surgery for an identical patient in one versus another random centre (Figure 2). This remained consistent when restricting to patients with both reactive pupils and a GCS < 15: proportion acute surgery ranging from 3·1 to 47·6% (IQR, 14·3-36·2%) between centres with a MOR of 1·7 ($p = 0·0244$). Furthermore, the a-priori reported thresholds for acute surgery, i.e. the centre treatment policies, were associated with the casemix-adjusted (observed) acute surgery rates, confirming that surgery rates reflect centre treatment preferences (Table 1 and appendix p 15).
Despite differences in baseline characteristics, the predicted 6-month functional outcome of the CRASH-CT score was similar across centres (Table 1), reflecting a

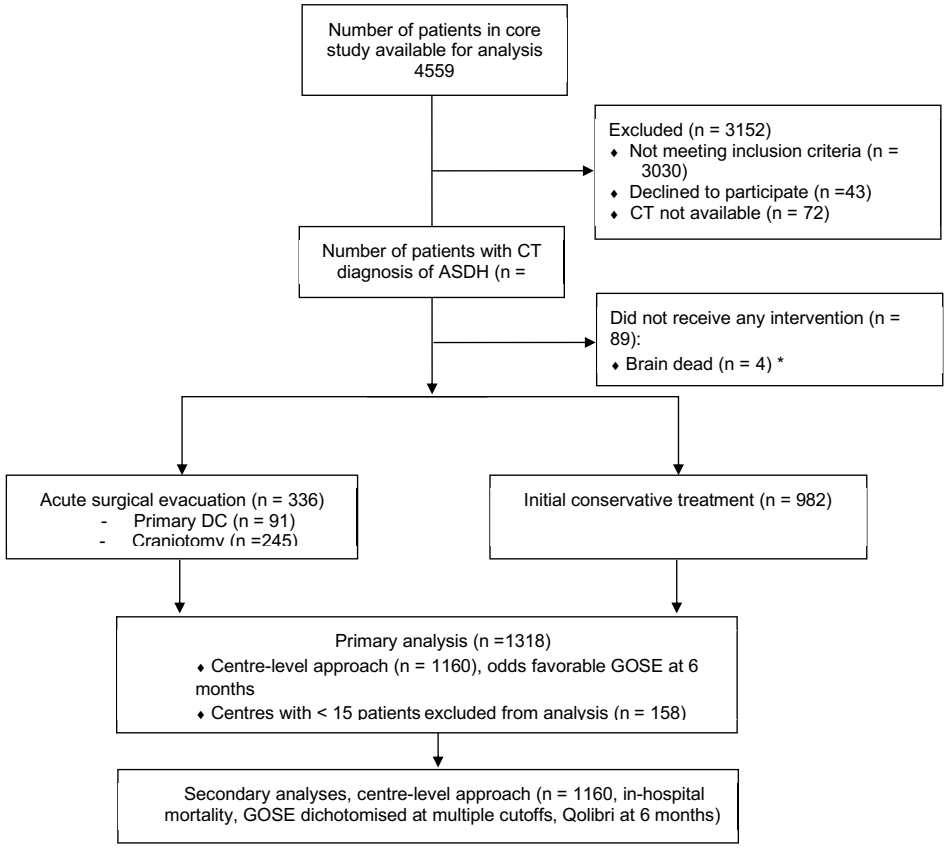


Figure 1. Flow diagram of study population and data analyses

* As judged by the treating physician.

DC indicates decompressive craniectomy, GOSE Glasgow Outcome Scale Extended and Qolibri Quality of Life after Brain Injury Scale.

balance in patient populations between centres with varying surgical preferences. Findings were consistent when analyses were restricted to patients with both reactive pupils and a GCS < 15 (appendix pp 29-32).

Formally, the testable assumptions for IV analyses were met (appendix p 33).

Thus, the widely differing surgical practices arise from centres that on average treat similar patients.

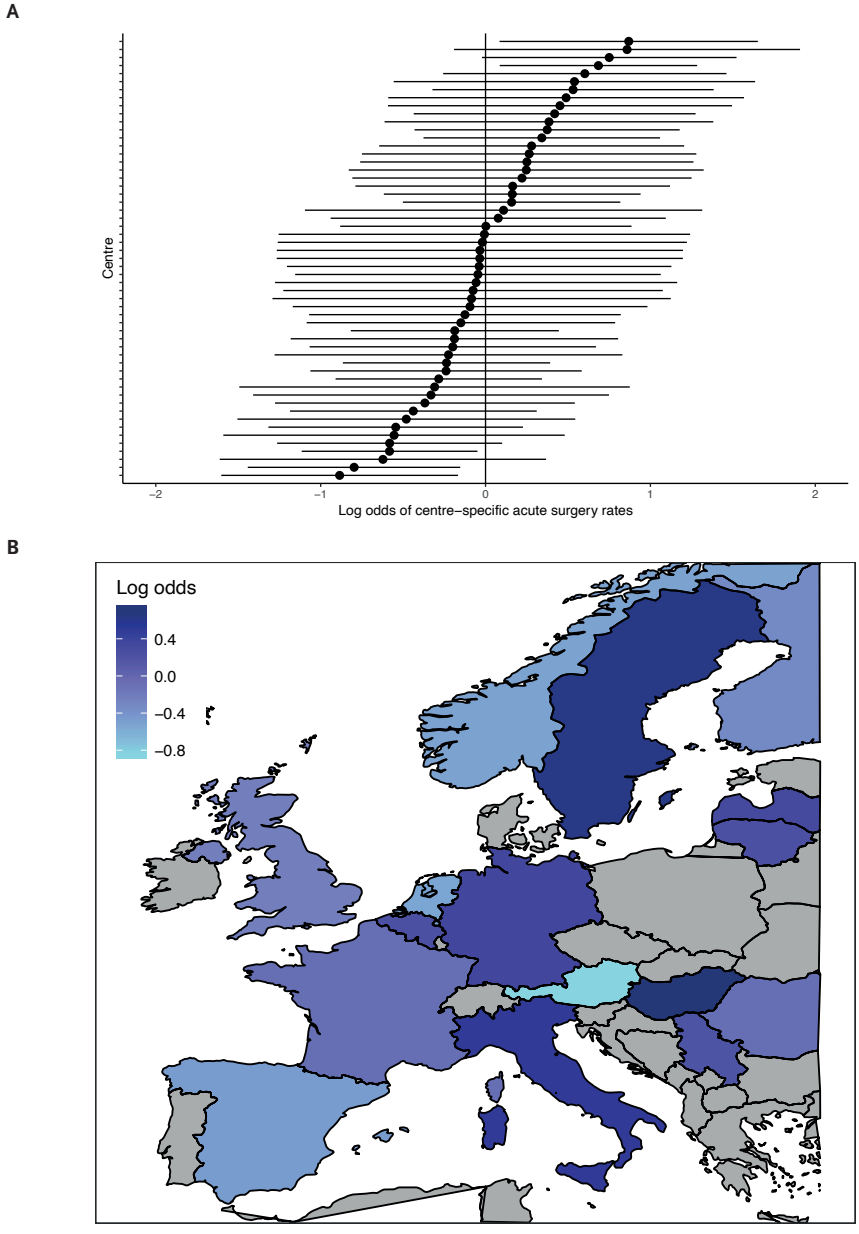


Figure 2. Between-centre (A) and between-country (B) differences in acute surgery

(A) The x-axis presents the log odds of the adjusted acute surgery rates per centre. A logistic random-effects model, adjusted for the predefined confounders age, GCS, pupil reactivity, hematoma size and midline shift, was used to estimate acute surgery preference per centre with corresponding 95% CIs. (B) The colour coding in this geographical representation of Europe depicts the log odds of acute surgery per country compared with the overall average, adjusted for confounding, by means of the same model used for the centre analysis.

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Number	229	348	291	292		
Age (median [IQR])	60 [43, 75]	52 [35, 66]	59 [36, 72]	59 [43, 71]	0·27	0·08
Sex					0·27	0·10
Female	77 (34)	97 (28)	117 (40)	84 (29)		
Male	152 (66)	251 (72)	174 (60)	208 (71)		
White European	195 (85)	292 (84)	248 (85)	244 (84)	0·51	0·28
Years of education (median [IQR])	12 [10, 15]	12 [9, 15]	12 [10, 15]	12 [10, 16]	0·36	0·09
College or university education	37 (16)	83 (24)	49 (17)	55 (19)	0·05	0·22
Married or living with partner	114 (50)	174 (50)	147 (51)	149 (51)	0·21	0·28
Working before injury (%)	97 (42)	138 (40)	116 (40)	125 (43)	0·25	0·27
ASAPS (%)					0·54	0·13
Healthy	106 (46)	164 (47)	157 (54)	135 (46)		
Mild systemic disease	90 (39)	129 (37)	85 (29)	111 (38)		
Severe systemic disease	27 (12)	46 (13)	42 (14)	32 (11)		
Threat to life	0 (0)	1 (0)	3 (1)	0 (0)		
Unknown	6 (3)	8 (2)	4 (1)	14 (5)		
History of cardiovascular disease	85 (37)	109 (31)	98 (34)	118 (40)	0·07	0·21
Alcohol consumption [b]	86 (38)	93 (27)	102 (35)	77 (26)	0·0150	0·19
Injury mechanism and cause					0·57	0·28
High velocity trauma	84 (37)	110 (32)	92 (32)	87 (30)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Incidental ground level fall	104 (45)	193 (55)	151 (52)	143 (49)		
Highest trained bystander (%)					0·55	0·23
None	15 (7)	19 (5)	17 (6)	15 (5)		
Untrained person (bystander)	1 (0)	6 (2)	6 (2)	2 (1)		
Paramedic	57 (25)	100 (29)	56 (19)	64 (22)		
Nurse	43 (19)	43 (12)	63 (22)	46 (16)		
Physician	59 (26)	92 (26)	72 (25)	79 (27)		
Medical rescue team	53 (23)	87 (25)	73 (25)	83 (28)		
Secondary referral (%)	59 (26)	85 (24)	75 (26)	65 (22)	0·41	0·08
Arrival Method (%)					0·19	0·22
Ambulance	167 (73)	268 (77)	212 (73)	216 (74)		
Helicopter	36 (16)	36 (10)	34 (12)	35 (12)		
Medical mobile team	11 (5)	23 (7)	18 (6)	26 (9)		
CPR (%)	8 (3)	12 (3)	10 (3)	4 (1)	0·19	0·14
IV Fluids (%)	86 (38)	129 (37)	121 (42)	124 (42)	0·30	0·10
Intubation (%)	70 (31)	97 (28)	88 (30)	97 (33)	0·63	0·08
Supplemental oxygen (%)	111 (48)	170 (49)	138 (47)	144 (49)	0·0221	0·24
Ventilation (%)	69 (30)	87 (25)	76 (26)	88 (30)	0·31	0·13
Hypoxia (%) [c]					0·54	0·13
No	204 (89)	279 (80)	263 (90)	248 (85)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Definite	9 (4)	20 (6)	19 (7)	17 (6)		
Suspect	7 (3)	9 (3)	2 (1)	10 (3)		
Hypotension (%) [d]					0·19	0·20
No	200 (87)	301 (86)	272 (93)	246 (84)		
Definite	18 (8)	12 (3)	6 (2)	18 (6)		
Suspect	2 (1)	4 (1)	7 (2)	7 (2)		
Any major extracranial injury (%) [e]	82 (36)	131 (38)	128 (44)	124 (42)	0·15	0·14
GCS baseline (median [IQR])	13 [4, 15]	12 [7, 15]	10 [6, 14]	11 [6, 14]	0·05	0·10
GCS motor baseline (median [IQR])	6 [1, 6]	6 [3, 6]	5 [1, 6]	5 [2, 6]	0·31	0·02
Pupils (%)					0·62	0·09
Both reacting	200 (87)	305 (88)	229 (79)	243 (83)		
One reacting	12 (5)	17 (5)	22 (7)	23 (8)		
Both unreacting	17 (7)	26 (7)	40 (14)	26 (9)		
Any focal neurological deficit (%)					0·29	0·14
No	149 (65)	233 (67)	190 (65)	208 (71)		
Yes	36 (16)	27 (8)	31 (11)	32 (11)		
Unknown	44 (19)	88 (25)	70 (24)	52 (18)		
Anti-coagulants or platelet aggregation inhibitors (%)					0·0128	0·31
No	162 (71)	271 (78)	216 (74)	205 (70)		
Anti-coagulants	31 (14)	20 (6)	29 (10)	18 (6)		

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)	p value	SMD
Platelet inhibitors	26 (11)	42 (12)	34 (12)	44 (15)		
Both	2 (1)	0 (0)	5 (2)	3 (1)		
Unknown	8 (3)	15 (4)	7 (2)	22 (8)		
Total volume of ASDH (cm3, median [IQR])	11 [3, 25]	14 [4, 31]	21 [6, 55]	17 [5, 53]	0·0001	0·39
CT ASDH = large (%) [f]	44 (19)	77 (22)	88 (30)	100 (34)	0·0002	0·34
CT midline shift (%) [g]	88 (38)	139 (40)	121 (42)	106 (36)	0·68	0·04
CT contusion (%)					0·59	0·12
No	95 (41)	122 (35)	128 (44)	104 (36)		
Small	105 (46)	187 (54)	126 (43)	148 (51)		
Large	28 (12)	38 (11)	30 (10)	39 (13)		
Unknown	1 (0)	1 (0)	7 (2)	1 (0)		
CT subarachnoid haemorrhage (%)					0·10	0·22
No	76 (33)	117 (34)	101 (35)	104 (36)		
Basal	13 (6)	31 (9)	23 (8)	26 (9)		
Cortical	115 (50)	158 (45)	132 (45)	118 (40)		
Basal and Cortical	25 (11)	42 (12)	35 (12)	44 (15)		
CT basal cisterns absent/compressed (%)	37 (16)	66 (19)	64 (22)	54 (18)	0·56	0·06
Mean predicted 6-month unfavourable outcome (GOS ≤ 3, %, median [IQR]) [h]	59 [31, 77]	48 [26, 65]	56 [31, 75]	56 [28, 73]	0·28	0·10
Centre characteristics						
Number of patients in academic hospital (vs. non- academic)	229 (100)	348 (100)	210 (72)	292 (100)	NA	<0·0001

Table 1. Baseline characteristics and prognostic risk across centres with different preferences for immediate treatment of acute subdural hematoma (*continued*)

	Treatment preference (percentages of patients having acute surgery per centre)*) [a]					
	Quartile 1 (<12%)	**Quartile 2 (12 – 22%)**	**Quartile 3 (23 – 36%)**	**Quartile 4 (>36%)**	**p value**	**SMD**
Number of beds (median (IQR))	925 [448, 1238]	841 [721, 1160]	953 [710, 1448]	898 [711, 1271]	0·59	0·43
Residency program neurosurgery	229 (100)	348 (100)	291 (100)	292 (100)	NA	<0·0001
Trauma centre designation					<0·01	0·58
- Level I	129 (70)	316 (95)	272 (100)	203 (100)		
- Level II	0 (0)	17 (5)	0 (0)	0 (0)		
- Level III	54 (30)	0 (0)	0 (0)	0 (0)		
Urban location (vs. suburban and rural location)	229 (100)	348 (100)	291 (100)	292 (100)	NA	<0·0001
Neurosurgeon staffing (FTE)	12 [10, 14]	12 [11, 12]	10 [8, 14]	7 [6, 11]	0·08	0·49
Number of surgeries for ASDH in 2013	62 [20, 99]	20 [14, 35]	24 [24, 25]	24 [8, 42]	0·16	0·60
Low threshold policy for acute surgery in ASDH [i]	46 (20)	66 (19)	170 (58)	179 (61)	<0·0001	0·92

Abbreviations: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; FTE, full time equivalent; GCS, Glasgow Coma Scale; GOS(E), Glasgow Outcome Scale Extended; IQR, interquartile range.

[a] Treatment preference as defined by the case-mix adjusted probability of undergoing acute surgery (as opposed to initial conservative treatment) based on the observed acute surgery rates per centre. The first category is less aggressive than the second and the second is less aggressive than the third and so forth. Importantly, the IV analysis used the acute surgery rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability.

[b] On presentation the behavioural history of the patient was recorded. This variable reflects the past three months consumption of alcoholic beverages (beer, wine, spirits) (>2/day).

[c] Second insult during the pre-hospital or ER phase, defined as partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg) or oxygen saturation of the arterial blood (SaO_2) < 90%. "Suspected" was scored if the patient did not have documented hypoxia by PaO_2 or SaO_2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[d] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. "Suspected" was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity).

[e] AIS □ 3.
[f] Large is defined as larger than 25 cm3.
[g] Midline shift present is classified as being more than 5 mm.
[h] TBI severity as summarized in predicted unfavourable outcome, proportion with a Glasgow Outcome Scale ≤ 3, based on CRASH-CT variables.
[i] Before patient inclusion in CENTER-TBI, treatment policies per centre were captured by provider profile surveys, including the policy towards acute surgery. The resulting threshold for acute ASDH surgery is dichotomized based on this distinction: 'Low', low threshold for surgery; 'High', high threshold for surgery).

Table 2. Primary and secondary outcomes and association with acute surgery

	Treatment preference (observed acute surgery rates)				Effect variable	Adjusted value (95% CI) [a]
	Quartile 1 (<12%)	Quartile 2 (12 – 22%)	Quartile 3 (23 – 36%)	Quartile 4 (>36%)		
Primary outcome: GOSE at 6 months (median [IQR])	5 [3 to 8)	6 [3 to 7]	5 [3 to 7]	5 [3 to 7)	Common odds ratio	0·92 (0·77 – 1·09)
Secondary outcomes						
In-hospital mortality	37 (16)	42 (12)	56 (19)	52 (18)	Odds ratio	1·04 (0·78 – 1·40)
GOSE of 7 or 8 (%)	92 (40)	128 (37)	88 (30)	96 (33)	Odds ratio	0·95 (0·76 – 1·12)
GOSE of 5-8 (%)	141 (57)	231 (66)	158 (54)	153 (53)	Odds ratio	0·88 (0·74 – 1·10)
GOSE of 4-8 (%)	163 (67)	249 (71)	183 (63)	165 (57)	Odds ratio	0·76 (0·61 – 0·99)
Qolibri (median [IQR]) at 6 months [b]	80 [64 to 92]	74 [62 to 83]	66 [51 to 86]	76 [64 to 85]	Beta	0·92 (-1·05 – 2·89)

Abbreviations: CI, confidence interval; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; Qolibri, Quality of Life after Brain Injury Scale;

[a] Estimates from random-effects multivariable logistic regression with the instrument, adjusted probability of performing acute surgery as treatment variable. Confounding was furthermore addressed by adjusting for the a-priori defined variables age, GCS, pupil reactivity, hematoma size and midline shift. The (common) odds ratio are presented as comparisons between the first quartile and the fourth quartile (IQR) of the instrument (the adjusted probabilities for undergoing acute surgery).

[b] Qolibri is a standardized health specific quality of life measure specifically designed for and validated for outcome assesment in patients with brain injury. It is a numerical scale with scores ranging from 0 to 100 with higher scores indicating a better quality of life. The score was available for 130 patients of the acute surgery group, 596 patients of the conservative management group.

Association with outcome

Centre preference for acute surgery over initial conservative treatment was not associated with better outcome according to GOSE at 6 months (adjusted common OR per 23·6% (IQR) more acute surgery in a centre 0·92 [95% CI 0·77-1·09], Table 2; appendix p 34). The ORs were consistent across multiple GOSE dichotomizations (Table 2). In the post-hoc analysis, excluding patients with one or two unreactive pupils and patients with GCS 15, the OR remained consistent (adjusted common OR per 22% (IQR) more acute surgery in a centre 0·91 [95% CI 0·72-1·18], appendix p 35). Subgroup analyses showed considerable practice variation and consistent ORs (appendix p 36). Centre preference for acute surgery was strongly, but non-significantly, associated with better outcomes in large hematomas (OR 2·7 [95% CI 0·86-8·32].

In sensitivity analyses, the association remained consistent when using the predefined instrumental variable (high vs low threshold surgical centres OR 1·05 [95% CI 0·85 – 1·32]), including centres with more than 10 patients instead of 15 (n = 1227, OR 0·87 [95% CI 0·66 – 1·0]), including the patients with a poor prognosis deemed to have an non-survivable injury (OR 1·01 [95% CI 0·87 – 1·27]) or excluding patients with unreactive pupils or GCS 15 (n = 730, OR 0·94 [95% CI 0·85 – 1·12], appendix p 37).

Adjustment in multivariable regression and propensity score matching gave comparable estimates to the primary analysis (appendix pp 37-40). Specifically excluding patients with one or two unreactive pupils and patients with GCS 15, the ORs from the multivariable regression and the propensity score matching remained consistent (appendix 37). In patient-level subgroup analyses, surgery was associated with worse outcome for age under 65. Acute surgery in the elderly and in patient with moderate TBI was non-significantly associated with better outcome (Figure 3). None of the secondary outcomes were different between groups (Table 2, appendix p 41).

DISCUSSION

In this comparative effectiveness study, similar patients with ASDH were treated differently due to varying surgical treatment preferences, and therefore, clinical equipoise can be inferred. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with a better outcome. Results were consistent when targeting patients in whom equipoise likely existed for surgical vs. conservative treatment.

In settings where RCTs are difficult to conduct and strong confounding by indication exists, observational studies using robust quasi-experimental approaches are a

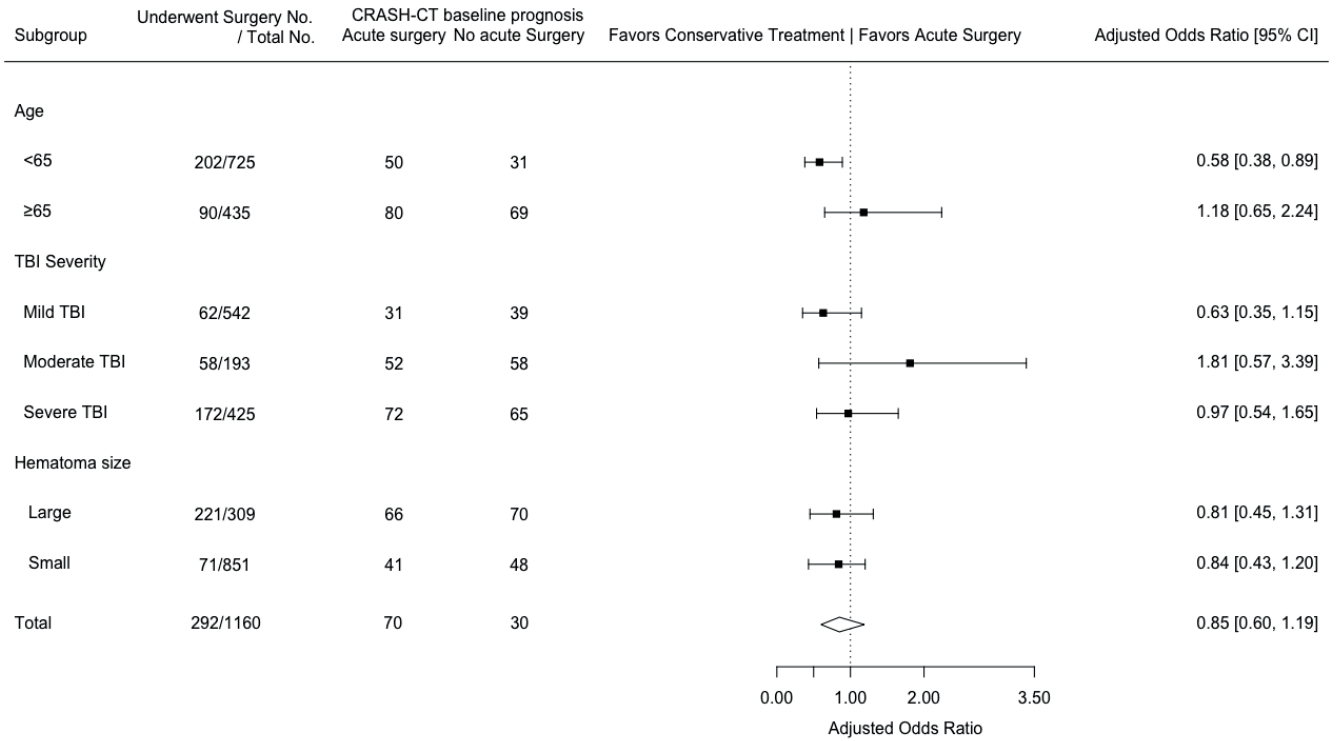


Figure 3. Subgroup analyses of the primary outcome for acute surgery, on patient-level

The panel shows the common odds ratio for an improvement on the ordinal Glasgow Outcome Scale Extended for acute surgery, stratified for subgroups, using ordinal logistic regressions with random-effects adjusted for predefined confounders. Baseline prognosis is summarized in the mean CRASH-CT predicted 6-month unfavourable outcome (GOS ≤ 3, %).

promising alternative.[26,27] The validity of our conclusions relies on whether the centre treatment rate is an appropriate instrumental variable. Our instrument was strongly associated with acute surgery and not associated with baseline prediction of outcome. The balanced confounding between centres allows to reliably infer a reasonable balance in the distribution of unmeasured confounding.[27] Yet, the observed practice variation might still partly result from residual prognostic differences. Therefore, we compared observed rates of surgery to centre policies captured during provider profiling and confirmed that the between-centre variation actually arises from provider preferences.[12] An a-priori reported low threshold for acute surgery was strongly associated with centres actually performing acute surgery more frequently for similar patients. Moreover, we showed that the organization of TBI care (in the same centres of the current study) was homogeneous, making residual confounding due to other local practice variations unlikely. To further disentangle the effect of the ASDH treatment strategy in a centre from other between-centre variations in care associated with outcome, the effect of the current treatment strategy on outcome was modelled with adjustment for other between-centre differences using a random-effect for centre.[27]

The findings were robust in predefined sensitivity analyses and subgroups. By excluding patients who, in the acute phase, did not receive active treatment due to poor prognosis, the results could have suffered from selection bias. Similar to cross-over in as-treated analysis in a RCT, the inclusion of this cohort for the effectiveness analyses may not have been independent from confounding.[32] However, we performed a sensitivity analysis on the entire cohort - thereby not selecting on treatment – and found a similar OR. Finally, immortal time bias has been addressed through the design in which we defined the treatment groups after the first CT (showing the ASDH), thereby aligning the start of the follow-up with treatment assignment.

In terms of clinical implication, the results should be interpreted more carefully than concluding no effect of surgery. First, estimating an overall effect of any (surgical) intervention in traumatic brain injury is amenable to a neutral result, possibly because of averaging heterogeneous effects.[33] In acute neurosurgery, several randomised controlled trials and comparative observational studies have found such negative findings. The reasons are multiple and might also be a variable response to treatment because of the complexity and variability of the injury.[34-37]

Second, the interpretation of IV effect estimates differs from that of conventional analyses. The instrument is the proportion surgically treated per centre as a proxy for the surgeon's treatment preference. Because an identical patient may be operated in one centre but not in another, it naturally follows that there is more than one valid treatment option. The results apply to patients for whom the neurosurgeon may be

in equipoise, judging that more than one valid treatment option exists (appendix p 17). As this equipoise differs per centre, we cannot readily identify the relative contribution of each subgroup.[38] Some authors suggest that IV analysis provides information on whether patients' outcome will improve when centres change their policy with respect to a specific intervention, rather than estimating an effect in individual patients.[39,40] In this study some extrapolation to patient-level effects may be appropriate, because the multivariable regression and propensity score matching resulted in similar estimates to the IV approach and all methods were reliable and implemented correctly.[31] The results should be appreciated in light of the conceptual difference between the employed methods.

Thus, although the inherent heterogeneous treatment effects in TBI and the indefinable patient population in IV effect estimation preclude recognizing an average treatment effect, the results suggest, when in equipoise regarding the decision to evacuate or not, no difference in outcome due to a centre's treatment strategy.

Surgical evacuation of ASDH remains the cornerstone of treatment in life-threatening neurological deterioration.[2] All patients with one nonreactive pupil and a large hematoma were surgically treated acutely in nearly all participating centres, which had also been confirmed in our treatment preference surveys.[10,12] The strong – albeit non-significant – IV effect of surgery in the predefined subgroup with large hematoma is consistent with clinical experience that most patients would probably die if not operated, an effect that cannot be deduced from a RCT due to obvious constraints.

The estimates in the age subgroups were consistent in patient- and centre-level analyses. A suggestion of benefit in the elderly is consistent with other comparative studies, although pre-existent co-morbidities are major drivers of outcome in the elderly with TBI.[41-43] The negative effect of acute surgery in patients younger than 65 rather contrasts the consensus of benefit of acute surgery in young ASDH patients. In general, acute surgery may not always be necessary and a substantial proportion of patients initially managed conservatively have satisfactory outcomes.[5-7,9,44]

This study's strengths are the comparative effectiveness design using a contemporary, large cohort, with prospective, standardized data collection and predefined provider profiling. A limitation already discussed is the difficulty in interpretation of IV analysis. A RCT would obviously be ideal but is not easily feasible and also has methodological challenges.[33] Another limitation remains the possible residual confounding due to other local practice variations associated with surgical threshold, despite statistical adjustment (i.e. random effects term), despite the study design construction (IV analysis with a-priori confirmed neurosurgeon's preferences), and despite robust association estimates. We previously performed, a separate cluster analysis, with

a broader medical domain view than neurosurgical treatment alone, to explore if the assumption of the absence of correlation between treatment choices holds.[21] The main conclusion was that, although correlations between treatment policies within domains (intracranial pressure monitoring, coagulation and transfusion, neurosurgery, prophylactic antibiotics, and more general ICU treatment policies) were found, is was not possible to cluster hospitals. Thus, specific treatment choices within the cohort do not correlate with other treatment choices of another domain. Importantly, the absence of correlation between domains was most pronounced for surgical treatment.

Limitation of the CENTER-TBI cohort in general is the focus on patients presenting to regional neurotrauma centres, with exclusion of pre-hospital deaths and patients with milder injuries. Participating institutions were mainly referral centres for neurotrauma and results might not be generalizable to other hospital settings and to every patient with a traumatic ASDH. For example, CENTER-TBI mainly included white males, reflecting the predominant white population of Europe and the fact that males are predominant in TBI, and thus the results are mostly applicable to white males.

An important power consideration is whether there could have been a clinically relevant treatment effect that was not detected with the current sample size. For power calculations the treatment effect was based on an OR 0.6, deduced from the available evidence, suggesting comparable effect sizes for surgical ASDH evacuation.[4,41,45] Nevertheless, this assumed treatment effect is substantial and also smaller effects might be clinically relevant. However, all analyses show robust odds ratios close to 1. The uncertainty in these estimates is reported through confidence intervals; not by claiming non-significance in the p-values. So, while larger sample sizes are desirable to reduce statistical uncertainty, the current results are highly relevant for clinical practice and reflects "real life" care among patients with ASDH referred to a dedicated neurotrauma centre.

Subsequent studies of surgery in ASDH are advised to be pragmatic RCTs, specifically targeted at those subgroups of patients likely to benefit from acute surgery, as explored in our study, in combination with previous evidence.

In conclusion, similar patients with traumatic ASDH, without an extremely poor or good prognosis at presentation, were treated differently across different centres due to varying treatment preferences. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with better outcome. Therefore, in a patient with an ASDH for whom a clinician sees no clear superiority in acute surgery versus conservative strategy, initial conservative treatment may be considered.

Contributors

TvE conceptualised the study, curated the data, analysed the data and drafted the manuscript including all tables and figures. DP assisted in the data curation. GdR, HL, ES, AM and WP assisted in the interpretation of the data and helped drafting the manuscript. AM, RW, GdR, WP (the clinical supervisors) and HL, ES (the statistical supervisors) supervised the methodology of the study protocol and supervised the study. TvE, HL, RW, ES, AM, GdR, and WP reviewed the manuscript multiple times. TvE, HL, VV, HdB, DM, PH, BD, ES, AM, GdR and WP were involved in the design of CENTER-TBI. All authors reviewed and approved the final version of the manuscript. TvE, DP and HL accessed and verified the analyses. All authors guarantee that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

AM declares consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. DKM reports grants from the UK National Institute for Health Research, during the conduct of the study; grants,
personal fees, and non-financial support from GlaxoSmithKline; and personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. EWS reports personal fees from Springer, during the conduct of the study. All other authors declare no competing interests.

Data sharing

The datasets, which include individual participant data and a data dictionary defining each field in the set used or analysed during the current study, will be available upon reasonable request to the management committee of the CENTER-TBI study. Requests for data should be submitted online at https://www.center-tbi.eu/data or via email to center-tbi@uza.be. The data that will be made available comprise de-identified participant data. The predefined study protocol is published.[14] The statistical analysis plan, R-syntax, and informed consent forms will be made available upon request. To access any other data from CENTER-TBI, a proposal should be submitted and approved by the management committees of the CENTER-TBI study. A data access agreement with the management team of CENTER-TBI should be signed before access to the data will be granted.

Acknowledgements

The authors' work on this study is funded by the *Hersenstichting Nederland* (the Dutch Brain Foundation, grant number ps2014.06) for the Dutch Neurotraumatology Quality Registry (Net-QuRe)[19] and the European Union seventh Framework Program (grant 602150) for CENTER-TBI. Additional support for CENTER-TBI was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA), from Integra LifeSciences Corporation (USA) and from NeuroTrauma Sciences (USA). We thank all patients for their participation in the CENTER-TBI study. We also thank all principal investigators and researchers for their collaboration and support.

See Online for appendix:
https://ars.els-cdn.com/content/image/1-s2.0-S1474422220016 61-mmc1.pdf

REFERENCES

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017;16(12):987–1048.
2. Munro D. The diagnosis and treatment of subdural hematoma. *N Engl J Med* 1934;210(22):1–16.
3. Servadei F, Compagnone C, Sahuquillo J. The role of surgery in traumatic brain injury. *Curr Opin Crit Care* 2007;13(2):163–8.
4. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; 58(3 Suppl):S16–24–discussionSi–iv.
5. Wong. Criteria for conservative treatment of supratentorial acute subdural haematomas. *Acta Neurochir Wien* 2005; (135):38–43.
6. Mathew P, Oluoch-Olunya DL, Condon BR, Bullock R. Acute subdural haematoma in the conscious patient: outcome with initial non-operative management. *Acta Neurochir* 1993;121(3-4):100–8.
7. Servadei F, Nasi MT, Cremonini AM, et al. Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural hematomas: a prospective study of 65 patients. *The Journal of Trauma: Injury, Infection, and Critical Care* 1998; 44(5):868–73.
8. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–92.
9. Feliciano CE, De Jesus O. Conservative management outcomes of traumatic acute subdural hematomas. *P R Health Sci J* 2008; 27(3):220–3.
10. Van Essen TA, De Ruiter GCW, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *Journal of Neurotrauma* 2017; 34(4):881–9.
11. Truong EI, Stanley SP, DeMario BS, et al. Variation in neurosurgical intervention for severe traumatic brain injury: The challenge of measuring quality in trauma center verification. *J Trauma Acute Care Surg* 2021; 91(1):114–20.
12. Van Essen TA, Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir* 2019; 161(3):435-449.
13. Lingsma HF, Roozenbeek B, Li B, et al. Large Between-Center Differences in Outcome After Moderate and Severe Traumatic Brain Injury in the International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury (IMPACT) Study. *Neurosurgery* 2011; 68(3):601–8.
14. Van Essen TA, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe. *BMJ Open* 2019; 9(10):e033513–8.
15. Von Elm E, Altman DG, Eggers M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet* 2007; 1453–7.
16. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013; 24(3):363–9.
17. McCulloch P, Altman DG, Flum DR, et al. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; 374(9695):1105–12.
18. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 2015; 76(1):67–80.
19. Nederlands Trial Register [Internet]. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.
20. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLoS ONE* 2016; 11(8):e0161367.
21. Ceyisakar IE, Huijben JA, Maas AIR, Lingsma HF, van Leeuwen N. Can We Cluster ICU Treatment Strategies for Traumatic Brain Injury by Hospital Treatment Preferences? *Neurocritical care* 2022; 36(3):846-856.
22. Commondataelements.ninds.nih.gov. National Institute of Neurological Disorders and Stroke.

23. Steyerberg EW, EW, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *The Lancet Neurology* 2019; 18(10):923–34.
24. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *Journal of Neurotrauma* 1998; 15(8):573–85.
25. Von Steinbuechel N, Petersen C, Bullinger M. Assessment of health-related quality of life in persons after traumatic brain injury--development of the Qolibri, a specific measure. *Acta Neurochir Suppl* 2005; 93:43–9.
26. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidem Drug Safe* 2010; 19(6):537–54.
27. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clinical Epidemiology* 2018;10:841–52.
28. Van Essen TA, Menon DK, Lingsma HF. Unmeasured Confounding in Observational Studies of Management of Cerebellar Intracranial Hemorrhage. *JAMA* 2020; 323(7):665–6.
29. MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 2008; 336(7641):425–9.
30. Boef AGC, Dekkers OM, le Cessie S, Vandenbroucke JP. Reporting instrumental variable analyses. *Epidemiology* 2013; 24(6):937–8.
31. Laborde-Castérot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. *Journal of Clinical Epidemiology* 2015;68(10):1232–40.
32. Swanson SA, Robins JM, Miller M, Hernán MA. Selecting on Treatment: A Pervasive Form of Bias in Instrumental Variable Analyses. *American Journal of Epidemiology* 2015; 181(3):191–7.
33. Maas AIR, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-Orientation of Clinical Research in Traumatic Brain Injury: Report of an International Workshop on Comparative Effectiveness Research. *Journal of Neurotrauma* 2012; 29(1):32–46.
34. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med* 2016; 375(12):1119–30.
35. Kuramatsu JB, Biffi A, Gerner ST, et al. Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage. *JAMA* 2019; 322(14):1392–12.
36. Shibahashi K, Sugiyama K, Tomio J, Hoda H, Morita A. In-hospital mortality and length of hospital stay with craniotomy versus craniectomy for acute subdural hemorrhage: a multicenter, propensity score-matched analysis. *Journal of Neurosurgery* 2019; 1–10.
37. Skolnick BE, Maas AI, Narayan RK, et al. A Clinical Trial of Progesterone for Severe Traumatic Brain Injury. *N Engl J Med* 2014; 371(26):2467–76.
38. Swanson SA, Hernán MA. The challenging interpretation of instrumental variable estimates under monotonicity. *International Journal of Epidemiology* 2017; 47(4):1289–97.
39. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; 297(3):278–85.
40. Maciejewski ML, Brookhart MA. Using Instrumental Variables to Address Bias From Unobserved Confounders. *JAMA* 2019; 321(21):2124–2.
41. Van Essen TA, Dijkman MD, Cnossen MC, et al. Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma in an Aging Population. *Journal of Neurotrauma* 2019; 1;36(7):1184-1191.
42. Shimoda K, Maeda T, Tado M, et al. Outcome and Surgical Management for Geriatric Traumatic Brain Injury: Analysis of 888 Cases Registered in the Japan Neurotrauma Data Bank. *World Neurosurg* 2014; 82(6):1300–6.
43. Younsi A, Fischer J, Habel C, et al. Mortality and functional outcome after surgical evacuation of traumatic acute subdural hematomas in octa- and nonagenarians. *European Journal of Trauma and Emergency Surgery* 2021; 47(5):1499-1510.
44. Gernsback JE, Kolcun JPG, Richardson AM, Jagid JR. Patientem Fortuna Adiuvat: The Delayed Treatment of Surgical Acute Subdural Hematomas-A Case Series. *World Neurosurg* 2018; 120:e414–20.
45. Seelig JM, Becker DP, Miller JD, et al. Traumatic acute subdural hematoma:

major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304(25):1511–8.

Chapter 11

Acute subdural hematoma: answering the clinically relevant question

Van Essen TA, Lingsma HF, Steyerberg EW, De Ruiter GCW, Maas AIR, Peul WC

The Lancet Neurol. 2022 Dec;21(12):1080-1081.

In this chapter I respond to a letter to the editor in which concerns are raised on the validity of our results from the effectiveness study of acute surgery in ASDH (Chapter 10).

We appreciate the comments of Nathan Beucler on our Article,[1] which possibly also reflect concerns shared by other neurosurgeons. In response to the first point, we restated the Brain Trauma Foundation guidelines regarding when to operate when a patient is not comatose. These guidelines for patients with a large haematoma (ie, clot >10 mm thick or causing >5 mm midline shift) recommend to operate regardless of the patient's Glasgow Coma Scale (GCS) score. Nevertheless, uncertainty about the best approach continues.

Second, Beucler suggests that delayed surgery could be regarded as acute surgery and should not have been analysed in the conservative treatment group. Our research question was whether to immediately operate on a patient with an acute subdural haematoma (on CT). This question reflects clinical reality. Some patients will deteriorate and have surgery later which— obviously—is not known at the time of planning. Comparison of all early (<24 h) surgical procedures with all conservatively treated patients would be erroneous and probably show that surgery leads to a worse outcome compared with conservative treatment, due to confounding by indication and immortal time bias. The Subdural Hematoma in the Elderly (SHE) Score[2] is an example of a study with such biases, at least when interpreted as an intervention instead of a prediction study. The SHE score is a prediction tool that should not be used to triage treatment—the extensively validated IMPACT and CRASH-CT models are superior in this respect. Moreover, the SHE score has limited value as a prediction tool for acute subdural haematoma because 31% of the cohort in that study had mixed-acuity or chronic subdural haematoma.[2] Therefore, the SHE score does not support an approach to limit treatment for older patients with acute subdural haematoma, with best available evidence suggesting the opposite.[3-5]

Third, Beucler presumes a benefit of primary decompressive craniectomy over craniotomy to account for the absence of benefit of acute surgery. No definitive evidence is available to support this assumption (while awaiting the findings of RESCUE-ASDH. Further, the author highlights the high proportion of decompressive craniectomy procedures in the conservative treatment group of total non-acute decompressive craniectomies, yet this metric does not inform the point. Instead, we should look at the proportion of decompressive craniectomy procedures in the (initially) conservatively treated group (52 of 982 patients had a delayed operation with a decompressive craniectomy, thus 5% is the risk of early secondary deterioration requiring decompressive craniectomy) and the proportion of delayed decompressive craniectomy procedures after a primary craniotomy (51 of 245 patients had decompressive craniectomy after primary craniotomy, a risk of 21%).

Beucler also comments that our inclusion criteria were too broad, and the multiple neurosurgery centres made interpretation difficult. We understand the difficulty of interpreting a comparative effectiveness study using instrumental variable analysis.

Since treatment allocation was based on neurosurgeon preference, the effect estimate is applicable to patients for whom the neurosurgeon would consider both treatment options. Sensitivity analyses with smaller inclusion criteria showed similar findings. We consider the multicentre nature of our study a strength, because studies with sufficient sample sizes can generate reliable and generalisable results.

REFERENCES

1 Van Essen TA, Lingsma HF, Pisică D, et al. Surgery versus conservative treatment fortraumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study. *The Lancet Neurol* 2022; 21: 620–31.

2 Alford EN, Rotman LE, Erwood MS, et al. Development of the Subdural Hematoma in the Elderly (SHE) score to predict mortality. *J Neurosurg* 2019; 132: 1616–22.

3 Van Essen TA, Dijkman MD, Cnossen MC, et al. Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population. *J Neurotrauma* 2019; 36: 1184–91.

4 Younsi A, Fischer J, Habel C, et al. Mortality and functional outcome after surgical evacuation of traumatic acute subdural hematomas in octa- and nonagenarians. *Eur J Trauma Emerg Surg* 2021; 47: 1499–510.

5 Valadka AB, Sprunt JM. Craniotomy for acute subdural hematoma in the elderly: not as bad as you thought. *World Neurosurg* 2012; 78: 231–2.

Chapter 12

Comparative effectiveness of decompressive craniectomy versus craniotomy for traumatic acute subdural hematoma: a CENTER-TBI study

Thomas A. van Essen, Inge A.M. van Erp, Hester Lingsma, Dana Pisica, Jeroen T.J.M. van Dijck, Victor Volovici, Angelos Kolias, Lianne D. Peppel, Majanka Heijenbrok-Kal, Gerard M. Ribbers, David K. Menon, Peter Hutchinson, Bart Depreitere, Ewout W. Steyerberg, Andrew I.R. Maas, Godard C.W. de Ruiter, Wilco C. Peul, and the CENTER-TBI Investigators and Participants

Under review

KEY POINTS

Question: Does primary decompressive craniectomy (DC) yield better outcome than craniotomy in patients surgically treated for a traumatic acute subdural hematoma (ASDH)?

Findings: In this international observational study of 336 ASDH patients from 65 centers, we found substantial practice variation in the employment of DC over craniotomy for ASDH. In an instrumental variable analysis, this variation in treatment strategy did not result in a difference in functional outcome on the Glasgow Outcome Scale-Extended scale at six months (primary outcome). However, primary DC was associated with higher in-hospital mortality, more follow-on surgeries, and more complications.

Meaning: Surgical ASDH evacuation by primary DC as opposed to craniotomy is unlikely to result in better outcomes.

ABSTRACT

Importance: Limited evidence exists on the comparative effectiveness of decompressive craniectomy (DC) versus craniotomy for evacuation of traumatic acute subdural hematoma (ASDH).

Objectives: To compare outcomes of primary DC versus craniotomy.

Design: Instrumental variable analysis of center treatment preference within the prospective observational Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury and Neurotraumatology Quality Registry studies, which enrolled patients throughout Europe and Israel (2014 to 2020).

Setting: International; multicenter.

Participants: Patients with a clinical and radiological ASDH and acute neurosurgery. Patients with severe pre-existing neurological disorders were excluded.

Exposures: Surgical ASDH evacuation with DC versus craniotomy.

Main outcomes: Functional outcome measured by the Glasgow Outcome Scale-Extended (GOSE) at 6 months. Analyses included random-effects ordinal regression with the adjusted center probability of DC as the instrumental variable.

Results: In 65 centers of 336 included patients, 91 (27%) underwent DC and 245 (63%) craniotomy for ASDH evacuation. The proportion of primary DC within total acute surgery cases ranged from 6-67% with an interquartile range (IQR) of 12-26% among 46 centers; odds of receiving a DC for prognostically similar patients in one center versus another randomly selected center were trebled (adjusted median odds ratio 2.7, $p < 0.0001$). Higher center preference for DC over craniotomy was not associated with better functional outcome (adjusted common odds ratio (OR) per 14% [IQR increase] more DC in a center = 0.9 [95% CI 0.7-1.1], n = 200). Primary DC was associated with more clinical complications (eg, higher rate of follow-on surgeries and complications [secondary cranial surgery 27% vs. 18%; shunts 11 vs. 5%]; and higher odds of in-hospital mortality (adjusted OR per 14% IQR more primary DC 1.3 [95% CI (1.0 – 3.5), n = 200].

Conclusions and relevance: In traumatic ASDH, surgical hematoma evacuation by primary DC is unlikely to result in better functional outcome at 6 months than craniotomy. Given greater risk of complications, primary DC should be restricted to salvageable patients in whom immediate replacement of the bone flap is not possible due to severe swelling.

INTRODUCTION

Acute subdural hematomas (ASDH) present in approximately one-third of patients with severe traumatic brain injury (TBI).[1,2] This space-occupying hematoma, can severely reduce blood flow to the brain, and elevate intracranial pressure (ICP), causing brain herniation, poor functional outcome, and death.[3] The decision to treat a patient surgically or conservatively in the acute phase turns on their neurological status, the size of the hematoma, and the degree of mass effect.[4]

Surgical procedure to evacuate ASDH follows one of two approaches: craniotomy with reconstruction of the skull with the bone flap replaced, or decompressive craniectomy (DC), in which the bone flap is not immediately rebuilt to mitigate (future) ICP increase. Several clinical scenarios guide the surgical decision. Primary DC is performed if, after ASDH evacuation, the brain swells beyond the skull intraoperatively, preventing safe replacement of the flap without pathological ICP rise. Another scenario is preventive, if there is concern that the brain may swell post-operatively.[5] Secondary DC is performed later in the clinical course, as a last-resort after exhaustion of neurocritical care measures, with clear benefits to functional outcomes.[6]

DC is considered more invasive than craniotomy, as it leads to a temporary bone defect, requires later skull reconstruction, and is associated with greater occurrence of post-traumatic hydrocephalus, bone flap reabsorption, and post-cranioplasty infection.[7] The Brain Trauma Foundation guideline for surgical treatment of ASDH provides no clear indication for selection of approach.[8]

Literature analyzing selection of technique has methodologic limitations, and comes largely from retrospective cohort studies.[1,4,9,10] This lack of high-quality evidence may lead to practice variation comparing neurosurgical centers, which may further confound results.[11,12] Comparative-effectiveness research (CER) can exploit this variation to determine optimal management.[13] In this observational study we compared primary DC versus craniotomy for ASDH, assessing functional outcome at 6 months, to test the hypothesis that primary DC yields better outcomes. This hypothesis is based on the most rigorous of the current evidence, which suggests better outcomes for primary DC.[14,15]

METHODS

The study and predefined protocol follow the Strengthening the Reporting of Observational Studies in Epidemiology statement with instrumental variable (IV) analyses recommendations, and corresponds to stage 3 in the IDEAL framework.[16,17]

Design

This is a prospective, observational, cohort study within the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI), which enrolled patients between 2014 and 2017 in 65 centers across Europe and Israel.[1] [18,19] Parent studies were conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95). Informed written or oral consent by patients or legal representatives was obtained according to local regulation.

Study population/data management

The CENTER-TBI cohort included patients with TBI and no pre-existing severe neurological disorders that could affect outcome assessment, who presented within 24 hours of trauma, and who had a brain CT ordered as part of clinical care. For the current study, we selected patients from the CENTER-TBI cohort with an ASDH confirmed on admission CT who received acute surgery.[2] We excluded patients who received a craniotomy for other types of injury, those that were brain dead, and those considered by the treating doctor to have an unsurvivable injury, for whom active treatment was futile. Data were collected by trained personnel using online case-report forms (QuesGen Systems, Burlingame, CA, USA), coded with the NIH-NINDS Common Data Elements.[18]

Center characteristics

Center characteristics have been previously reported.[11] Questions included center policy regarding the threshold for primary DC, which was used in sensitivity analyses. Other treatment decisions possibly related to surgical threshold (eg, prehospital care) could affect the internal validity of the study. We therefore did a cluster analysis, showing that center surgical treatment preferences were unrelated to other treatment preferences.[20]

Interventions

Acute hematoma evacuation was performed via craniotomy or primary DC, at the discretion of the treating neurosurgeon. Treatment groups were classified according to first (presenting) CT. Per study protocol, neurosurgeons were queried as to reason(s) surgery was indicated, surgical approach, and confirmed according to operating room disposition and by intervention codes or description. Techniques for durotomy and potential duroplasty were not routinely collected. Other emergency

1 The CENTER-TBI patients enrolled in The Netherlands were co-enrolled in the Neurotraumatology Quality Registry (Net-QuRe), which enrolled patients between 2015 and 2020 in 7 centers across the Netherlands. Net-QuRe had identical eligibility criteria but included patients with a Glasgow Coma Scale (GCS) score < 13.

and post-surgical care followed local protocols (ICU management, ICP monitoring, and/or follow-on surgery).

Outcomes

The primary outcome was functional outcome at 6 months on the Glasgow Outcome Scale-Extended (GOSE).[21] Secondary outcomes were in-hospital mortality, ICP, frequency and type of neurosurgical interventions, medical and surgical complications, 'treatment failure' (subsequent craniotomy or DC), ICU and hospital length of stay (days), dichotomized 6-month GOSE score across multiple thresholds, and quality of life at 6-months postinjury, measured with the Quality of Life after Brain Injury instrument (QOLIBRI).[22]

Statistical analysis

Baseline characteristics are presented using descriptive statistics, including standardized mean differences across the instrument and between groups. The CRASH-CT head injury model was used to calculate predicted probabilities of unfavorable outcome.[23] We calculated the median odds ratio (MOR) to compare between-center differences in surgery. The MOR quantifies treatment variation between centers that is not attributable to chance and not explained by other (case-mix) factors.

Outcomes were analyzed with respect to center treatment strategy (and not actual treatment) using instrumental variable (IV) analyses. In this natural experiment the IV "allocates" patients to either the DC or craniotomy treatment strategy based on the treating center, and reduces (unmeasured) confounding (eMethods).

The common odds ratio (OR) was estimated with a random-effects multivariable proportional odds logistic regression model with the ordinal GOSE as outcome variable, the case-mix adjusted center-specific treatment probability of DC as the independent variable (the IV), and a random intercept for treating center (unexplained residual between-center differences). The OR summarizes the shift in the direction of a better score on the GOSE. Adjustment was made for age, GCS, pupillary reactivity, midline shift, concomitant contusion, and hematoma size as potential confounders. The resulting adjusted common OR was presented as an increase from the first to the fourth quartile (IQR) of the (continuous) instrumental variable (the adjusted probabilities for undergoing DC) and can be interpreted as the odds of a more favorable outcome when comparing centers favoring a strategy of primary DC versus those favoring craniotomy. Only centers with □ 10 patients were included in analyses.

Sensitivity analysis included IV analysis using center-preference for primary DC as the instrumental variable, per prior published provider profile.[11] Sensitivity IV analysis

was also performed excluding centers with < 15 patients. Last, the IV association of surgical preference with outcome was also estimated by linear regression with the case-mix adjusted probability of DC (treatment preference) as the independent variable, mean GOSE by center as the dependent variable, and similar adjustment.
We performed unadjusted and multivariable regression and propensity score matching (PSM) as sensitivity analyses with actual DC received as treatment variable (yes/no; not center DC preference) and GOSE as ordinal outcome variable. We determined adjusted ORs (aOR) for multiple cutoff values on the GOSE to assess consistency of effect estimates. Further details are supplemented (eMethods). Analyses were conducted using R-software 4.1.0, RStudio 1.1.463. Missing data were multiply imputed ('mice' package, m=5), assuming data to be missing-at-random. The 95% CIs for the ORs were obtained from 2.5 and 97.5 percentiles among the bootstrap replications.

RESULTS

Of 4509 patients in CENTER-TBI, 336 patients underwent acute surgery for an ASDH, of whom 91 (27%) received a primary DC and 245 (73%) received a craniotomy (Figure 1). Median time from injury to start of surgery was 3.5 hours for primary DC (IQR 2.2–5.1) and 4.1 hours for craniotomy (IQR 2.8-7.0). Patients undergoing primary DC were younger (median age 49 vs. 59 years), less often on anticoagulants and/or platelet aggregation inhibitors (14 vs. 25%), with more major extracranial injuries (53 vs. 36%), worse presenting GCS scores (median 4 vs. 7), larger ASDH volumes (median 64 vs. 49 cm^3), and more frequent contusions and subarachnoid hemorrhages (66% vs. 55%, and 75% vs. 62% respectively; eTable 1).
These baseline characteristics did not translate into different predicted 6-month unfavorable outcomes calculated according to the CRASH-CT for primary DC compared to craniotomy (respectively, 71 vs. 74 %). The most frequently cited rationale for selecting a DC was a 'pre-emptive approach to treatment of (suspected) raised ICP (not last resort)' in 31% of DC cases (eTable 2).
Secondary DC or craniotomy for contusions or hematomas was performed in 25 (27%) patients initially treated with primary DC and in 43 (18%) patients initially treated with craniotomy. Patients undergoing primary DC vs. craniotomy had longer hospital stays (median 38 vs. 18 days), more frequently required shunts (11 vs. 5%), and had more intracranial complications (delayed intracranial hematoma/seroma, 23 vs. 16%). Cranioplasty during primary admission was performed in 23 (25%) patients in the primary DC group and in 12 (5%) in the craniotomy group (after secondary DC) (eTable 3).

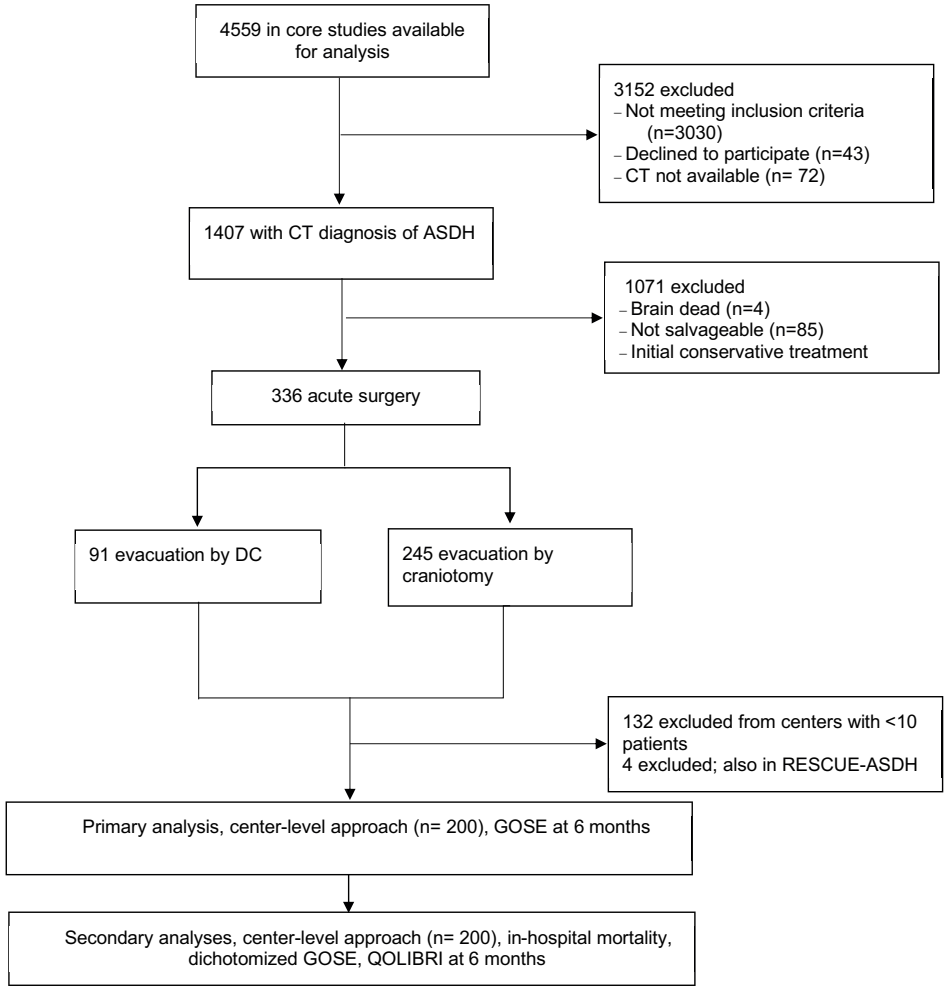


Figure 1. Flow diagram of study population and data analyses

DC: decompressive craniectomy, GOSE: Glasgow Outcome Scale Extended, QOLIBRI, Quality of Life after Brain Injury Questionnaire.

The proportion of primary DC relative to all acute surgeries ranged from 6% to 67% across 46 centers (IQR = 12-26%; Figure 2A), with a MOR of 2.7 ($p < 0.0001$) (Figure 2B and 2C), representing an almost 3-fold higher odds of receiving DC for clinically similar patients, when randomly comparing 2 centers. Moreover, baseline prognosis (predicted 6-month unfavorable outcome of the CRASH-CT score) for surgical patients across regions defined by primary DC treatment rates were similar (Table 1). The testable assumptions for IV analyses were met (eResults).

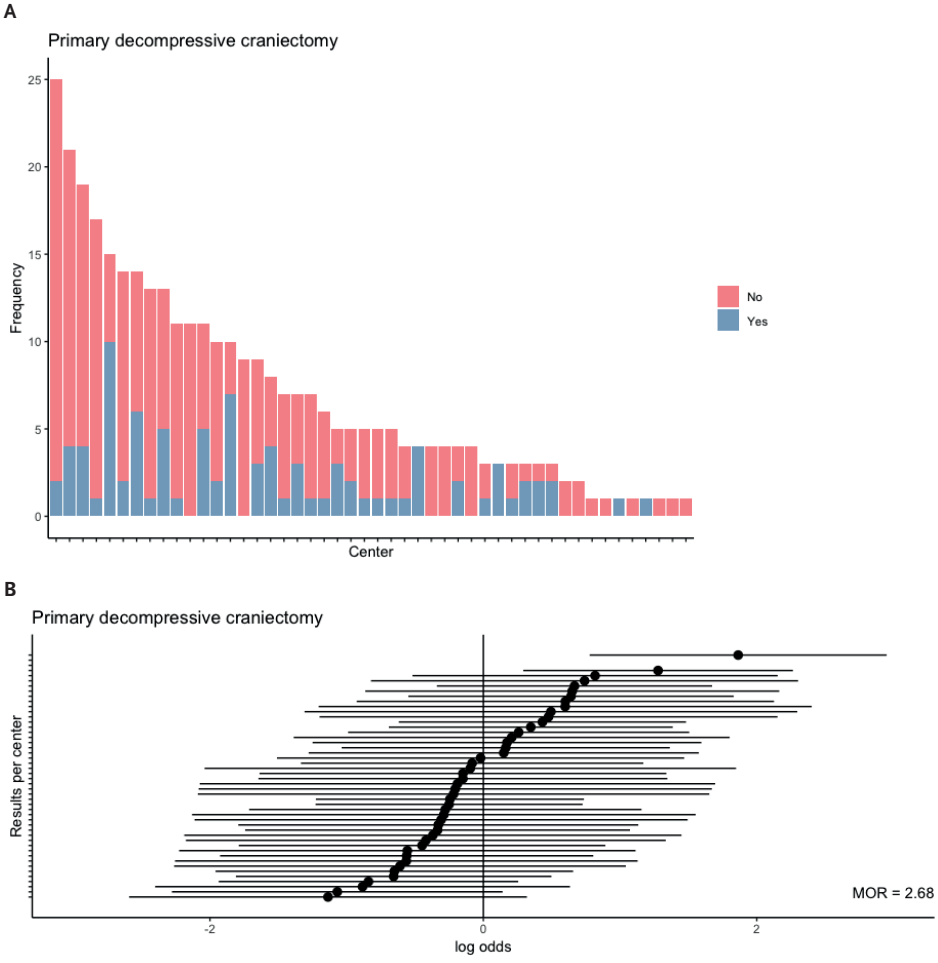


Figure 2. Between-center and between-country differences in primary decompressive craniectomy

Figure 2A shows the observed frequencies of primary decompressive craniectomy of surgical ASDH patients per center. Figure 2B shows the case-mix adjusted log odds ratio for primary decompressive craniectomy per center (A). The median odds ratio (MOR) reflects the between-center variation; a MOR equal to 1 represents no variation, the larger the MOR, the larger the variation. The MOR is 2.7 (p value < 0.0001).

C

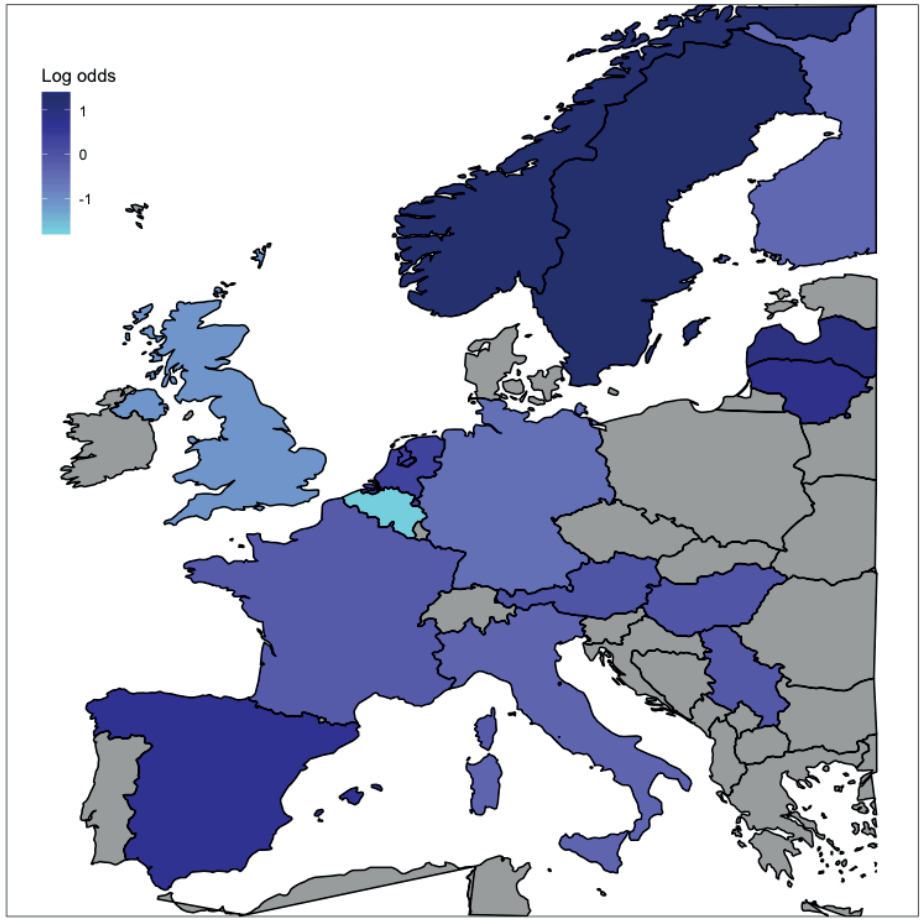


Figure 2. Between-center and between-country differences in primary decompressive craniectomy *(continued)*

Figure 2C represents the log odds ratio for primary decompressive craniectomy as compared to craniotomy per country compared with the overall average, also case-mix adjusted.

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	Quartile 2 (12 – 19%)	Quartile 3 (19 – 26%)	Quartile 4 (26 - 67%)	SMD
n	53	48	51	48	
Age (median [IQR])	63 [56, 69]	56 [43, 66]	56 [38, 68]	53 [34, 64]	0.26
ASAPS (%)					0.44
Healthy	28 (53)	17 (35)	28 (55)	23 (48)	
Mild systemic disease	21 (40)	16 (33)	14 (27)	15 (31)	
Severe systemic disease	4 (8)	11 (23)	7 (14)	7 (15)	
Threat to life	0 (0)	0 (0)	1 (2)	0 (0)	
Unknown	0 (0)	4 (8)	1 (2)	3 (6)	
Hypoxia (%) [b]					0.49
No	41 (77)	42 (88)	44 (86)	37 (77)	
Definite	1 (2)	1 (2)	5 (10)	6 (12)	
Suspect	2 (4)	4 (8)	1 (2)	2 (4)	
Unknown	9 (17)	1 (2)	1 (2)	3 (6)	
Hypotension (%) [c]					0.44
No	41 (77)	46 (96)	46 (90)	39 (81)	
Definite	2 (4)	1 (2)	3 (6)	2 (4)	
Suspect	1 (2)	0 (0)	1 (2)	3 (6)	
Unknown	9 (17)	1 (2)	1 (2)	4 (8)	
Any major extracranial injury (%) [d]	23 (43)	15 (31)	28 (55)	25 (52)	0.27
GCS baseline (median [IQR])	9 [4, 13]	7 [3, 11]	5 [3, 9]	6 [3, 11]	0.30
GCS motor baseline (median [IQR])	5 [2, 6]	4 [1, 5]	1 [1, 4]	2 [1, 5]	0.43

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy (*continued*)

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	**Quartile 2 (12 – 19%)**	**Quartile 3 (19 – 26%)**	**Quartile 4 (26 - 67%)**	**SMD**
Pupils (%)					0.32
Both reacting	36 (68)	35 (73)	32 (63)	28 (58)	
One reacting	3 (6)	7 (15)	9 (18)	10 (21)	
Both unreacting	14 (26)	6 (12)	10 (20)	10 (21)	
Total volume of ASDH (cm3, median [IQR])	58 [31, 97]	70 [40, 114]	70 [32, 103]	50 [18, 79]	0.24
CT large ASDH (%) [e]	35 (66)	37 (77)	42 (82)	31 (65)	0.25
CT midline shift (%) [f]	42 (79)	38 (79)	48 (94)	44 (92)	0.29
CT contusion (%)					0.40
No	19 (36)	25 (52)	21 (41)	23 (48)	
Small	24 (45)	19 (40)	23 (45)	13 (27)	
Large	10 (19)	3 (6)	6 (12)	11 (23)	
Unknown	0 (0)	1 (2)	1 (2)	1 (2)	
CT subarachnoid haemorrhage (%)					0.37
No	18 (34)	21 (44)	12 (24)	21 (44)	
Basal	5 (9)	2 (4)	6 (12)	2 (4)	
Cortical	22 (42)	15 (31)	27 (53)	16 (33)	
Basal and cortical	8 (15)	10 (21)	6 (12)	9 (19)	
CT basal cisterns absent/compressed (%)	20 (38)	19 (40)	25 (49)	21 (44)	0.13
Mean predicted 6-month unfavourable outcome (GOS score ≤ 3, %, median [IQR]) [g]	74 [52, 86]	73 [53, 87]	80 [67, 91]	69 [51, 84]	0.22
Center characteristics					
Academic hospital (vs. non- academic, %)	0 (0)	0 (0)	0 (0)	14 (29)	0.45

Table 1. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy (*continued*)

	Treatment preference (observed primary DC rates per centre) [a]				
	Quartile 1 (6 - 12%)	**Quartile 2 (12 – 19%)**	**Quartile 3 (19 – 26%)**	**Quartile 4 (26 - 67%)**	**SMD**
Number of beds (median [IQR])	655 [600, 850]	1083 [1018, 1148]	1170 [936, 1292]	780 [652, 831]	0.80
Residency program neurosurgery (%)	53 (100)	48 (100)	51 (100)	48 (100)	<0.01
Level I trauma center designation (%)	42 (100)	48 (100)	51 (100)	35 (100)	<0.01
Urban location (vs. suburban and rural location, %)	53 (100)	48 (100)	51 (100)	48 (100)	<0.01
Neurosurgeon staffing (FTE, median [IQR])	11 [8, 19]	11 [10, 12]	10 [6, 12]	8 [8, 11]	0.50
Number of surgeries for ASDH in 2013 (median [IQR])	28 [10, 30]	18 [16, 20]	62 [20, 102]	25 [22, 25]	0.82
Number of surgeries for contusion in 2013 (median [IQR])	7 [5, 8]	10 [7, 14]	15 [4, 236]	10 [8, 14]	0.37
Low threshold policy for primary DC in ASDH (%) [h]	0 (0)	0 (0)	0 (0)	24 (50)	0.71

Abbreviation: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale (5-point); IQR, interquartile range; IV, instrumental variable; SMD, standardized mean difference.

[a] Treatment preference as defined by the case-mix adjusted probability of undergoing primary DC (as opposed to craniotomy) based on the observed primary DC rates per centre. This corresponds to the IV status and presented in quartiles of the range of adjusted regional primary DC rates. The first category is less aggressive than the second and the second is less aggressive than the third and so forth. Importantly, the IV analysis used adjusted primary DC rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability.

[b] Second insult during the pre-hospital or ER phase, defined as $PaO_2 < 8$ kPa (60 mmHg)/$SaO_2 < 90\%$. 'Suspected' was scored if the patient did not have documented hypoxia by PaO_2 or SaO_2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[c] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. 'Suspected' was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity)

[d] AIS □ 3

[e] Large is defined qualitatively by the treating neurosurgeon and corresponded to a size larger than 25 cm^3.

[f] Midline shift present is classified as being more than 5 mm.

[g] TBI severity as summarized in predicted unfavorable outcome, proportion with a Glasgow Outcome Scale ≤ 3, based on CRASH-CT variables age, GCS score, pupillary reactivity to light, major extracranial injury, and CT characteristics (midline shift >5mm, traumatic subarachnoid hemorrhage, and obliteration of the basal cisterns).

[h] Before patient inclusion in CENTER-TBI, treatment policies per center were captured by provider profile surveys, including the policy towards primary DC. The resulting threshold for primary DC is dichotomized based on this distinction: Yes', primary DC routinely/pre-emptively versus 'No', no primary DC routinely/pre-emptively.

Table 2. Primary and secondary outcomes and treatment associations for primary decompressive craniectomy

Outcome	Adjusted center-level analyses					
	Treatment preference (observed primary DC rates per centre)				Effect variable	Adjusted value (95% CI) [a]
	Quartile 1 (6 - 12%, n = 53)	Quartile 2 (12 – 19%, n = 48)	Quartile 3 (19 – 26%, n = 51)	Quartile 4 (26 - 67%, n = 48)		
Primary outcome: GOSE at 6 months (median [IQR])	3 [1 to 7]	3 [1 to 6]	3 [1 to 6]	3 [1 to 6]	Common odds ratio	0.9 (0.7 – 1.1)
Secondary outcomes						
In-hospital mortality	12 (23)	11 (23)	21 (41)	18 (38)	Odds ratio	1.3 (1.0 – 3.4)
GOSE of 7 or 8 (%)	13 (25)	10 (21)	7 (14)	8 (17)	Odds ratio	0.9 (0.7 – 1.2)
GOSE of 5-8 (%)	17 (32)	20 (42)	16 (31)	17 (35)	Odds ratio	1.0 (0.8 – 1.2)
GOSE of 4-8 (%)	20 (38)	21 (44)	19 (37)	22 (46)	Odds ratio	1.0 (0.8 – 1.2)
QOLIBRI (median [IQR]) at 6 months [b]	Na [c]					

Abbreviation: CI, confidence interval; DC, decompressive craniectomy; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; Na, not available; QOLIBRI, Quality of Life after Brain Injury Scale.

[a] Estimates from random-effect multivariable ordinal/logistic regression with the instrument, adjusted probability of undergoing primary DC as treatment variable. Confounding was furthermore addressed by adjusting for the a-priori defined variables age, GCS, pupil reactivity, hematoma size, contusion presence and midline shift. The adjusted common OR indicates the odds of a higher GOSE score (primary outcome) or experiencing the secondary outcomes, for an increase from the 25th percentile to the 75th percentile of the range in exposure to the center intervention preferences.

[b] QOLIBRI is a standardized health specific quality of life measure specifically designed for and validated in outcome assesment in patients with brain injury. It is a numerical scale with scores ranging from 0 to 100, with higher scores indicating a better quality of life. The score was available for 19 patients of the primary DC group and 111 of the craniotomy group.

[c] The association could not be estimated due to low numbers (no centers with □ 10 patients in the subcohort).

After excluding patients from centers with < 10 patients (n = 132), 200 patients were available for primary IV analysis (Table 1). Center preference for DC over craniotomy was not associated with better functional outcome (adjusted common OR 0.9, 95% CI 0.7 – 1.1 in favor of craniotomy, Table 2, eFigure 2). The aORs were consistent across GOSE cutoffs (Table 2). In-hospital mortality was associated with a higher center preference for primary DC (aOR per 14% IQR more primary DC 1.3 [95% CI (1.0 – 3.4), Table 2). The association between surgical strategy and quality of life could not be estimated due to low numbers (no centers with □ 10 patients in the QOLIBRI subgroup).

Patients from centers with the highest case-mix adjusted probability (ie, preference for) DC more often had a period of neuroworsening and a higher Therapy Intensity Level (TIL). Otherwise, secondary outcomes did not differ between surgical preference groups (eTable 5).

Primary DC was associated with worse outcomes in unadjusted patient-level analysis (eg, GOSE: common OR 0.4, 95% CI 0.3 – 0.6; eTable 6, eTable 7). Covariable adjustment in multivariable regression and PSM (at patient-level) resulted in GOSE-association estimates favoring a craniotomy (adjusted common OR 0.4, 95% CI 0.2 – 0.6 and adjusted common OR 0.4, 95% CI 0.3 – 0.8, respectively; eFigure 1, eTable 6, eTable 8). In sensitivity IV analyses, the primary association estimate remained consistent when excluding centers with < 15 patients (n = 97; adjusted common OR 0.9 [95% CI 0.5 – 1.5], eTable 6, 9, 10 and 11), and when using *a priori* defined IV (adjusted common OR 0.9, 95% CI 0.4 – 2.2; eTable 6). In-hospital mortality did not differ across centers with primary DC preference in sensitivity IV analysis excluding centers with < 15 patients (eTable 10).

DISCUSSION

This prospective observational study demonstrates large treatment variation across European and Israeli centers in the selection of DC versus craniotomy in surgical evacuation of traumatic ASDH. It is the first to exploit this variation using IV analyses, finding that primary DC compared to craniotomy was unlikely to be associated with better functional outcome. These findings held in predefined IV sensitivity analyses. Patient-level analysis with multivariable regression and PSM revealed poorer outcomes for primary DC, although as described below, residual confounding may have been present. Further, primary DC was associated with more complications, more follow-on surgeries and higher in-hospital mortality.

Election of primary DC is well established in cases of ASDH with acutely severe swelling preventing replacement of the bone flap. A recent consensus states that if the brain is bulging beyond the inner table of the skull intra-operatively, the bone

flap should not be replaced.[8,24] The advantage of a DC is more effective control of ICP elevation, potentially preventing secondary brain injury and poor clinical outcome. However, DC necessitates additional reconstructive surgery (cranioplasty) and carries risks related to the bone defect, infections, and bone-flap reabsorption.[7] Further, DC is known to alter cerebrospinal fluid flow dynamics, and cerebral blood flow dynamics, both of which improve with replacement of the bone flap.[25-28] Clinically relevant evidence is weak for primary DC in ASDH; large treatment variations exist,[11,29,30] and support for claims of effectiveness are inconsistent. Most of these observational studies suggest worse outcomes for primary DC.[1,4,9,10,15,31,32] When comparing the preoperative and baseline characteristic of DC versus craniotomy cohorts, all studies show that patients selected to undergo DC are more likely to have lower GCS, more concomitant hematomas and therefore, and have a poorer prognosis at baseline. Neurosurgeons are therefore more likely to select DC for the more severely impaired patients in anticipation of potential cerebral swelling that is difficult to manage medically. The higher number of patients with poor prognosis undergoing DC suggests strong confounding within these observational studies and that interpretation of worse outcomes resulting from primary DC, rather than from worse baseline status, may be incorrect.[5,13] The methodologically best – albeit small - study evaluating this treatment variation through comparison of two neurosurgical centers found postoperative ICP to be better controlled and outcomes improved in the centers with greater utilization of primary DC in TBI.[14] However, these results included patients undergoing emergent DC or craniotomy for any mass or diffuse lesion, not specifically ASDH, which represented only 15 of 52 participants.

Our findings confirm these previously reported treatment variations and the inconsistency displayed by neurosurgeons as to selection of primary DC versus craniotomy in the absence of massive swelling. Patients in our cohort who underwent primary DC were also more severely injured, despite scoring similar prognoses on CRASH-CT, and required more interventions to lower ICP (ie, greater TIL). Although many patients who received primary DC attained similar 6-month GOSE outcomes as patients who received craniotomy, as noted, they experienced a worse clinical course. We maintain that the chance of a favorable outcome after primary DC was less likely when viewed in the context of the IV analyses, which showed an absence of clear benefit, and the patient-level analyses that clearly suggested harm.

Comparative effectiveness research with IV analysis, utilizing heterogeneity in practices across centers to compare their effectiveness of interventions that may be standard practice in some centers, but not in others, offers complementary evidence to the gold standard of RCTs.[33,13,34] Compared with conventional, patient-level analysis, IV CER is less prone to confounding. The validity, however, relies on whether the center treatment rate is an appropriate instrumental variable. Our instrument was

strongly associated with primary DC and did not associate with baseline prognosis: the widely differing surgical strategies are practiced in centers that on average treat similar patients. The balanced confounding between centers suggests a reasonable balance in the distribution of unmeasured confounding.[13] Nonetheless, the observed practice variation might still partly result from prognostic differences. Therefore, we surveyed providers to evaluate whether the between-center variation actually arose from provider preferences.[11] The *a priori* reported center policy for primary DC strongly predicted actual primary DC use (ie, stronger than any single patient characteristic). To further extricate the effect of the ASDH surgical strategy in a center from other between-center care variations associated with outcome, we adjusted with a random-effects for center.

The totality of our analyses suggests that the chance of a favorable outcome after primary DC is less likely when viewed in the context of the IV analyses, which showed an absence of clear benefit, and the patient-level analyses that clearly suggested harm. Given the higher risk of a complicated clinical course, we maintain that the selection of primary DC should be restricted to salvageable patients with brain swelling precluding flap repositioning. Our results apply to patients for whom the neurosurgeon may be in equipoise, because, an identical patient may receive a DC in one center and a craniotomy in another, it naturally follows that there is more than one valid treatment option. And since equipoise differs per center, we cannot readily identify the relative contribution of each subgroup.[35-37]

We acknowledge several limitations. First, possible residual confounding remains due to other local practice variations associated with surgical preference, despite IV analysis, rigorous statistical adjustment (ie, a random-effects term) and multiple sensitivity analyses, particularly the IV analysis with the *a priori* center policy for approach as a different, strong IV, strongly correlated to the actual DC employment, confirming consistent neurosurgeon's preferences. To further account for center-level confounding we performed a separate cluster analysis, with a broader medical domain view than neurosurgical treatment alone, to explore if the assumption of the absence of correlation between treatment choices is tenable. The main conclusion was that specific treatment policies within domains (ICP monitoring, coagulation and transfusion, neurosurgery, prophylactic antibiotics, and more general ICU treatment policies) do not correlate with other treatment policies. Importantly, the absence of correlation between domains was most pronounced for surgical treatment. Another limitation is that participating institutions of CENTER-TBI were mainly tertiary referral centers. Results may not be generalizable to other hospital settings and every patient. Last, the interpretation of the effect of primary DC is hampered by the relatively small sample size, resulting in a wide confidence interval that may obscure

a small, clinically relevant effect. Although this cohort is the largest to date, subgroup analyses were considered infeasible.

CONCLUSION

In patients with a traumatic ASDH, surgical evacuation by primary DC as compared to craniotomy is unlikely to be of benefit, measured in terms of functional outcome at 6 months, and the higher risk of complications. Our study underscores the necessity of collecting granular data on interventions and their sequelae to more accurately delineate the clinical course. The pragmatic RESCUE-ASDH RCT will provide further evidence on the efficacy of primary DC for ASDH.[38] Strong consideration should be given to revising guidelines to restrict selection of primary DC to patients whose severe swelling precludes replacement of the bone flap. Such direction could bring needed evidence-based consistency to current practice and result in better overall outcomes for patients.

Funding/Support: The authors' work on this study is funded by the *Hersenstichting Nederland* (the Dutch Brain Foundation, grant number ps2014.06) for the Dutch Neurotraumatology Quality Registry (Net-QuRe)[19] and the European Union seventh Framework Program (grant 602150) for CENTER-TBI. Additional support for CENTER-TBI was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (USA), from Integra LifeSciences Corporation (USA) and from NeuroTrauma Sciences (USA).

Role of the Funder/Sponsor: The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgements: The authors thank Amy J. Markowitz, JD (Editorial Consultant and Program Manager Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI), Brain and Spinal Injury Center, Zuckerberg San Francisco General Hospital, Department of Neurological Surgery, University of California San Francisco, The United States of America) for critical appraisal of our manuscript.

REFERENCES

1. Woertgen C, Rothoerl RD, Schebesch KM, Albert R. Comparison of craniotomy and craniectomy in patients with acute subdural haematoma. *J Clin Neurosci* 2006;13(7):718-721.
2. van Essen TA, Lingsma HF, Pisică D, et al. Surgery versus conservative treatment for traumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study. *Lancet Neurol* 2022; 21(7):620-631.
3. Yang C, Ma Y, Xie L, et al. Intracranial Pressure Monitoring in the Intensive Care Unit for Patients with Severe Traumatic Brain Injury: Analysis of the CENTER-TBI China Registry. *Neurocrit Care* 2022; 37(1):160-171.
4. Tsermoulas G, Shah O, Wijesinghe HE, et al. Surgery for Acute Subdural Hematoma: Replace or Remove the Bone Flap? *World Neurosurg* 2016; 88:569-575.
5. Phan K, Moore JM, Griessenauer C, et al. Craniotomy Versus Decompressive Craniectomy for Acute Subdural Hematoma: Systematic Review and Meta-Analysis. *World Neurosurg* 2017; 101:677-685.e672.
6. Kolias AG, Adams H, Timofeev IS, et al. Evaluation of Outcomes Among Patients With Traumatic Intracranial Hypertension Treated With Decompressive Craniectomy vs Standard Medical Care at 24 Months: A Secondary Analysis of the RESCUEicp Randomized Clinical Trial. *JAMA Neurol* 2022; 79(7):664-671.
7. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurg Focus*. 2009;26(6):E7.
8. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurger.* 2006;58(3 Suppl):S16-24; discussion Si-iv.
9. Rush B, Rousseau J, Sekhon MS, Griesdale DE. Craniotomy Versus Craniectomy for Acute Traumatic Subdural Hematoma in the United States: A National Retrospective Cohort Analysis. *World Neurosurg* 2016; 88:25-31.
10. Ahmed N, Greenberg P, Shin S. Mortality Outcome of Emergency Decompressive Craniectomy and Craniotomy in the Management of Acute Subdural Hematoma: A National Data Analysis. *Am Surg* 2021; 87(3):347-353.
11. van Essen TA, den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir (Wien)* 2019; 161(3):435-449.
12. van Essen TA, de Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; 34(4):881-889.
13. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clin Epidemiol* 2018; 10:841-852.
14. Hartings JA, Vidgeon S, Strong AJ, et al. Surgical management of traumatic brain injury: a comparative-effectiveness study of 2 centers. *J Neurosurg* 2014; 120(2):434-446.
15. Li LM, Kolias AG, Guilfoyle MR, et al. Outcome following evacuation of acute subdural haematomas: a comparison of craniotomy with decompressive craniectomy. *Acta Neurochir (Wien)* 2012; 154(9):1555-1561.
16. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet* 2007; 370(9596):1453-1457.
17. Van Essen TA, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe. *BMJ Open* 2019;9(10):e033513.
18. Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; 76(1):67-80.
19. Peppel LD, Heijenbrok-Kal MH, Van Essen TA, et al. A delphi procedure on rehabilitation outcome for patients with moderate to severe traumatic brain injury; first phase of the Neurotraumatology Quality Registry (NeT-QuRe). *J Rehabil Med* 2022; 54:jrm00249.
20. Ceyisakar IE, Huijben JA, Maas AIR, et al. Can We Cluster ICU Treatment Strategies for Traumatic Brain Injury by Hospital Treatment Preferences? *Neurocrit Care* 2022;36(3):846-856.

21. Hudak AM, Caesar RR, Frol AB, et al. Functional outcome scales in traumatic brain injury: a comparison of the Glasgow Outcome Scale (Extended) and the Functional Status Examination. *J Neurotrauma* 2005; 22(11):1319-1326.
22. Kreitzer N, Jain S, Young JS, et al. Comparing the Quality of Life after Brain Injury-Overall Scale and Satisfaction with Life Scale as Outcome Measures for Traumatic Brain Injury Research. *J Neurotrauma* 2021; 38(23):3352-3363.
23. Han J, King NK, Neilson SJ, Gandhi MP, Ng I. External validation of the CRASH and IMPACT prognostic models in severe traumatic brain injury. *J Neurotrauma* 2014; 31(13):1146-1152.
24. Hutchinson PJ, Kolias AG, Tajsic T, et al. Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury: Consensus statement. *Acta Neurochir (Wien)* 2019; 161(7):1261-1274.
25. Won YD, Yoo DS, Kim KT, et al. Cranioplasty effect on the cerebral hemodynamics and cardiac function. *Acta Neurochir Suppl* 2008; 102:15-20.
26. Halani SH, Chu JK, Malcolm JG, et al. Effects of Cranioplasty on Cerebral Blood Flow Following Decompressive Craniectomy: A Systematic Review of the Literature. *Neurosurgery* 2017; 81(2):204-216.
27. Stiver SI, Wintermark M, Manley GT. Motor trephine syndrome: a mechanistic hypothesis. *Acta Neurochir Suppl*. 2008;102:273-277.
28. Czosnyka M, Copeman J, Czosnyka Z, et al. Post-traumatic hydrocephalus: influence of craniectomy on the CSF circulation. *J Neurol Neurosurg Psychiatry* 2000; 68(2):246-248.
29. Mohan M, Layard Horsfall H, Solla DJF, et al. Decompressive craniotomy: an international survey of practice. *Acta Neurochir (Wien)* 2021; 163(5):1415-1422.
30. Kolias AG, Scotton WJ, Belli A, et al. Surgical management of acute subdural haematomas: current practice patterns in the United Kingdom and the Republic of Ireland. *Br J Neurosurg* 2013; 27(3):330-333.
31. Chen SH, Chen Y, Fang WK, Huang DW, Huang KC, Tseng SH. Comparison of craniotomy and decompressive craniectomy in severely head-injured patients with acute subdural hematoma. *J Trauma* 2011;71(6):1632-1636.
32. Shibahashi K, Sugiyama K, Tomio J, Hoda H, Morita A. In-hospital mortality and length of hospital stay with craniotomy versus craniectomy for acute subdural hemorrhage: a multicenter, propensity score-matched analysis. *J Neurosurg* 2019:1-10.
33. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312(7040):1215-1218.
34. Timmons SD, Toms SA. Comparative effectiveness research in neurotrauma. *Neurosurg FOCUS* 2012; 33(1):E3.
35. Stukel TA, Fisher ES, Wennberg DE, et al. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007; 297(3):278-285.
36. Maciejewski ML, Brookhart MA. Using Instrumental Variables to Address Bias From Unobserved Confounders. *JAMA*. 2019; 321(21):2124-2125.
37. Swanson SA, Hernán MA. The challenging interpretation of instrumental variable estimates under monotonicity. *Int J Epidemiol* 2018; 47(4):1289-1297.
38. Kolias AG, Adams H, Timofeev I, et al. Decompressive craniectomy following traumatic brain injury: developing the evidence base. *Br J Neurosurg* 2016; 30(2):246-250.

SUPPLEMENTARY CONTENT

eMETHODS

Instrumental variable analysis

The main analysis associates center-level treatment strategies to functional outcome to deduce effectiveness. This natural experiment, in which patients are 'allocated' to one or another treatment strategy based on where the accident occurred, leads to considerable reduction of (unmeasured) confounding because patients are brought to hospitals without knowledge of neurosurgical treatment preference. This is an instrumental variable (IV) analysis, a quasi-experimental approach, where the IV center 'allocates' patients to be exposed to different likelihoods of receiving primary decompressive craniectomy (DC). IV analysis is less biased by (unmeasured) confounding by indication and is the preferred analytical method in observational studies on acute neurosurgical decisions in traumatic brain injury.[1-3]

The IV approach accounts for unmeasured confounding for which two verifiable assumptions must be met: 1) the instrument is associated with the intervention, and 2) the instrument is not independently associated with the outcome.[4] The first assumption was addressed using the median odds ratio (MOR), which quantifies the between-center primary DC variation that is not explained by other factors in the model or attributable to chance. A fixed-effects logistical regression model was compared to a model with random intercept for center (with age, GCS score, pupil reactivity, midline shift, concomitant contusion and hematoma size as fixed-effects in both models) with the likelihood ratio test to determine the significance of between-center variation and the partial F statistic as a measure for explained variance.[3] The second assumption was addressed by comparing baseline prognosis (CRASH-CT score) across the levels of the IV. Moreover, associations between the IV and measured confounders were checked by calculating Spearman's correlation coefficients between the IV (center preference) and predicted probabilities of unfavorable outcome.

For the IV analyses, the (common) ORs of primary and secondary endpoints are presented as an incremental increase from the 25th percentile to the 75th percentile (the interquartile range [IQR]) of the adjusted primary DC probabilities (treatment preference). The resulting adjusted OR indicates the odds of a more favorable outcome for patient in a hospital at the 25th percentile compared to a patient in a hospital at the 75th percentile on the range of the center surgical preference. To minimize the influence of chance, centers with data on at least 10 patients were included in the primary IV analyses which was a deviation from our protocol.[5] The protocol stated to include centers contributing at least 15 patients but that resulted in considerably smaller sample. The study protocol was published before patient enrollment.[5]

Sensitivity analyses

As sensitivity IV analysis, the instrument was compared with prior collected data on preference for a pre-emptive and/or routine approach with regard to DC when evacuating ASDH from the provider profiling of the CENTER-TBI study.[6]

Additional analyses were performed with primary DC defined at patient-level (exposed to intervention, yes/no), unadjusted, with multivariable regression and propensity score matching (PSM) and restricting to the BTF-guideline subgroup. The propensity of being exposed to the intervention was computed using multivariable logistic regression with primary DC as dependent variable. PSM was used to match exposed patients with non-exposed patients. The maximum difference between propensity scores was set at 0.10 (the caliper) using a nearest neighbor approach in 1:1 balance. For both the propensity score model and the covariable-adjusted model, the aforementioned confounding variables of the primary analysis were considered independent variables. We used random-effects models with center as the clustering variable for all patient-level analyses.

eRESULTS

Quantification of practice variation and instrumental variable assumptions

The instrument was consequently strongly associated with the intervention under study (partial F statistic 28; eTable 2). Further, correlations between the instruments and measured confounders were small (Spearman's Rho correlation -0.17; eTable 4), meaning that despite differences in baseline characteristics, the predicted 6-month functional outcome of the CRASH-CT score was similar across centers. The a-priori reported policy of a low threshold for primary DC was the strongest predictor of observed primary DC, i.e. over and above all other predictors (OR 8.8, 95% CI 1.9 – 40.0, as compared to e.g. variable 'two nonreactive pupils' with OR 1.4, 95% CI 0.5 – 4.0), confirming that primary DC rates reflect center treatment preferences (Table 1).

Sensitivity analyses

On a continuous outcome scale in linear regression, higher adjusted primary DC rates per center were not associated with higher mean GOS-E scores. For an increase from the 25th to the 75th percentile (i.e. the IQR) of the adjusted probabilities for primary DC, the mean GOSE decreased non-significantly with 0.1 for primary DC (95% CI: -0.2 – 0.1); eFigure 2). In a similar analysis excluding centers with < 15 patients the mean GOSE increased non-significantly with 0.1 for primary DC (95% CI: -1.1 – 1.4)).

eTable 1. Baseline and treatment characteristics of patients with acute surgery for traumatic acute subdural hematoma, comparing primary decompressive craniectomy and craniotomy

Patient characteristic		Treatment (n = 336)			
		Decompressive craniectomy	Craniotomy	SMD	Missing (%)
n		91	245		
Age (median [IQR])		49 [35, 62]	59 [42, 68]	0.42	0
Male sex (%)		73 (80)	169 (69)	0.24	0
ASAPS (%)				0.40	0
Healthy		51 (56)	108 (44)		
Mild systemic disease		18 (20)	88 (36)		
Severe systemic disease		13 (14)	36 (15)		
Threat to life		1 (1)	1 (0)		
Unknown		8 (9)	11 (5)		
Injury cause (%)				0.33	0
Road traffic incident		29 (33)	67 (29)		
Incidental fall		44 (49)	114 (49)		
Other non-intentional injury		2 (2)	9 (4)		
Assault/violence		7 (8)	15 (6)		
Suicide attempt		3 (3)	3 (1)		
Hypoxia (%) [a]				0.36	1
	No	66 (75)	201 (82)		
	Definite	12 (14)	12 (5)		
	Suspect	6 (7)	10 (4)		
	Unknown	4 (5)	21 (9)		
Hypotension (%) [b]				0.10	1
	No	76 (87)	205 (84)		
	Definite	3 (4)	12 (5)		
	Suspect	4 (5)	10 (4)		
	Unknown	5 (6)	17 (7)		
Any major extracranial injury (%) [c]		48 (53)	89 (36)	0.34	0
GCS (median [IQR])		4 [3, 8]	7 [3, 13]	0.50	5
GCS motor (median [IQR])		1 [1, 4]	4 [1, 6]	0.53	2
Pupils (%)				0.26	4
Both reacting		53 (59)	162 (70)		
One reacting		13 (14)	31 (13)		
Both unreacting		24 (27)	38 (17)		
Any focal neurological deficit (%)				0.39	0
No		33 (36)	124 (51)		
Yes		12 (13)	43 (18)		
Unknown		46 (51)	77 (32)		
Anti-coagulants or platelet aggregation inhibitors (%)				0.31	0
No		71 (78)	164 (67)		

eTable 1. Baseline and treatment characteristics of patients with acute surgery for traumatic acute subdural hematoma, comparing primary decompressive craniectomy and craniotomy (*continued*)

Patient characteristic	Treatment (n = 336)			
	Decompressive craniectomy	Craniotomy	SMD	Missing (%)
Anti-coagulants	5 (6)	28 (12)		
Platelet inhibitors	8 (9)	30 (12)		
Both	0 (0)	3 (1)		
Unknown	7 (8)	19 (8)		
Total volume of ASDH (cm3, median [IQR])	64 [34, 97]	49 [20, 83]	0.32	32
CT large ASDH (%) [d]	69 (76)	183 (75)	0.03	0
CT midline shift (%) [e]	79 (87)	208 (85)	0.06	0
CT contusion (%)			0.28	0
No	28 (31)	106 (43)		
Small	38 (42)	94 (38)		
Large	21 (23)	39 (16)		
Unknown	3 (3)	6 (2)		
CT SAH (%)			0.38	0
No	23 (25)	94 (38)		
Basal	6 (7)	20 (8)		
Cortical	38 (42)	97 (40)		
Basal and Cortical	24 (26)	34 (14)		
CT basal cisterns absent/compressed (%)	50 (56)	106 (44)	0.24	1
Mean predicted 6-month unfavorable outcome (GOS score ≤ 3, %, median [IQR]) [f]	71 [59, 86]	74 [50, 87]	0.11	0
Acute surgery characteristics				
Surgery type		Na		9
Hemi-craniectomy	79 (87)			
Bifrontal-craniectomy	4 (5)			
Time from injury to surgery (minutes, median [IQR])	210 [131, 303]	246 [165, 420]	0.11	1

Abbreviation: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale (5-point); ICP, intracranial pressure; IQR, interquartile range; SAH, subarachnoid hemorrhage; SMD, standardized mean difference.

[a] Second insult during the pre-hospital or ER phase, defined as PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. "Suspected" was scored if the patient did not have documented hypoxia by PaO2 or SaO2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnea or respiratory distress.

[b] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. "Suspected" was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity).

[c] AIS □ 3

[d] Large is defined qualitatively by the treating neurosurgeon and corresponded to a size larger than 25 cm³.

[e] Midline shift present is classified as being more than 5 mm.

[f] TBI severity as summarized in predicted unfavorable outcome, proportion with a Glasgow Outcome Scale score ≤ 3, based on CRASH-CT variables.

eTable 2. Characteristics of primary decompressive craniectomy

Patient characteristic		
		Missing
n	91	
Reason for DC (%)		10
Pre-emptive approach to treatment of (suspected) raised ICP (not last resort)	25 (31)	
Raised ICP, refractory to medical management (last resort)	17 (21)	
ICP not monitored, but CT evidence of raised ICP	21 (26)	
Not directly planned, but decided on because of intra-operative brain swelling	14 (17)	
Routinely performed with every ASDH or contusion evacuation	4 (5)	
Development of cerebral infarction	1 (1)	

Abbreviation: ASDH, acute subdural hematoma; DC, decompressive craniectomy; ICP, intracranial pressure

eTable 3. Hospital course, complications and follow-up of patients with acute surgery for traumatic acute subdural hematoma, comparing primary decompressive craniectomy and craniotomy

	Treatment (n = 336)			
	Decompressive craniectomy	**Craniotomy**	**SMD**	**Missing (%)**
n	91	245		
Length of hospital stay (median [IQR])	38 [24, 67]	18 [10, 36]	0.42	0
Any neuroworsening (%) [a]	48 (53)	100 (41)	0.23	0
Progression on CT (%) [b]	36 (40)	83 (34)	0.10	1
Increase in initial lesion	26 (72)	50 (60)		
Development of new lesion	10 (28)	32 (39)		
Secondary surgery (%)	25 (27)	43 (18)		27
DC	14 (56)	12 (28)		
ASDH	9 (36)	23 (53)		
Contusion/ICH	2 (8)	8 (190		
Time injury to secondary or delayed surgery (min, median [IQR])	795 [466, 29090]	1210 [330, 4310]		
ICP monitor (%)	79 (87)	157 (64)	0.55	0.0
ICP (median [IQR])	12 [9, 17]	12 [8, 15]	0.23	32
CPP (median [IQR])	74 [70, 77]	73 [67, 77]	0.02	32
TIL (median [IQR])	8 [6, 12]	3 [1, 7]	1.01	2
Extracranial surgery (%)	25 (28)	44 (18)	0.23	0
Other cranial surgery (during admission, after primary surgery or initial conservative treatment, %)				
Epidural hematoma	4 (4)	7 (3)		
Ventriculostomy for CSF drainage	12 (13)	23 (9)		
Chronic subdural hematoma	1 (1)	0 (0)		

eTable 3. Hospital course, complications and follow-up of patients with acute surgery for traumatic acute subdural hematoma, comparing primary decompressive craniectomy and craniotomy (*continued*)

	Treatment (n = 336)			
	Decompressive craniectomy	Craniotomy	SMD	Missing (%)
Cranioplasty	23 (25)	12 (5)		
CSF shunt	10 (11)	12 (5)		
Complications (requiring treatment)				0
Delayed intracranial hematoma/seroma (%)	21 (23)	40 (16)	0.17	
Raised ICP (%)	50 (55)	84 (34)	0.43	
Meningitis (%)	11 (12)	16 (7)	0.19	
Seizure (%)	11 (12)	31 (13)	0.02	
Other intracranial complication %)	9 (10)	14 (6)	0.16	
Ventilator-associated pneumonia (%)	24 (26)	32 (13)	0.34	
Cardiac arrest (%)	7 (8)	17 (7)	0.03	
Respiratory (%)	21 (23)	50 (20)	0.07	
Cardiovascular (%)	2 (2)	11 (5)	0.13	
Metabolic (%)	10 (11)	12 (5)	0.23	
CRBSI (%)	4 (4)	7 (3)	0.08	
Deep venous thrombosis (%)	4 (4)	7 (3)	0.08	
Pulmonary embolus (%)	3 (3)	5 (2)	0.08	
Pressure sores (decubitus) (%)	10 (11)	15 (6)	0.18	
Urinary tract infection (%)	8 (8)	22 (9)	0.01	
Other systemic complication (%)	11 (12)	31 (13)	0.02	
Discharge destination			0.36	38
Other hospitalw	12 (25)	49 (32)		
Rehabilitation unit	22 (46)	61 (40)		
Nursing home	5 (10)	10 (7)		
Home	5 (10)	27 (18)		
Other	4 (8)	5 (3)		
Treatment during follow-up (after discharge)				0
Hydrocephalus	7 (8)	2 (1)		
Chronic subdural hematoma	2 (2)	4 (2)		
Cranioplasty	14 (15)	11 (4)		

Abbreviation: DC, decompressive craniectomy; CRBSI, catheter-related bloodstream infection; CSF, cerebrospinal fluid; ICP, intracranial pressure IQR, interquartile range; TIL, Therapy Intensity Level.

[a] Neuroworsening is defined as: a spontaneous decrease in the Glasgow Coma Scale motor score ≥ 2 points (compared with the previous examination), a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm, and/or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.

[b] Progression on the CT scan during the hospital course is defined as an increase in initial lesion and/or the development of a new lesion.

eTable 4. Assumptions for instrumental variable analyses

IV assumptions	*Primary DC*
Assumption 1: instrument association with intervention	
Partial F statistic	28.3
Assumption 2: instrument association with prognosis	
Spearman's Rho correlation with $P_{Unfavorable}$ [a]	-0.17

Abbreviation: DC, decompressive craniectomy; IV, instrumental variable

[a] Prognosis as summarized in CT-CRASH score, predicted unfavorable outcome (proportion with a Glasgow Outcome Scale score ≤ 3)

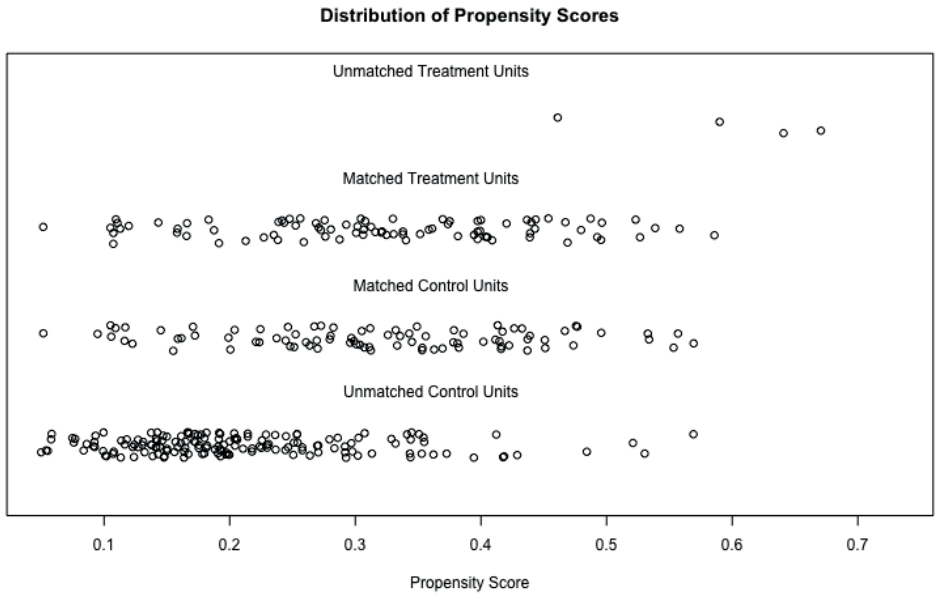
eTable 5. Hospital course and outcome across centers with different preferences for primary decompressive craniectomy

	Treatment preference (observed acute surgery rates)				
	Quartile 1 (6 - 12%)	**Quartile 2 (12 – 19%)**	**Quartile 3 (19 – 26%)**	**Quartile 4 (26 - 67%)**	**SMD**
n	53	48	51	48	
Any neuroworsening (%) [a]	23 (43)	13 (27)	27 (53)	32 (67)	0.45
Progression on CT (%) [b]	22 (42)	15 (31)	21 (41)	21 (44)	0.13
ICP monitor placement (%)	44 (83)	25 (52)	34 (67)	37 (77)	0.38
ICP (median [IQR])	12 [8, 15]	11 [8, 16]	10 [7, 17]	12 [7, 16]	0.10
CPP (median [IQR])	68 [61, 73]	71 [65, 76]	72 [67, 76]	74 [69, 76]	0.07
TIL (median [IQR])	5 [2, 8]	3 [1, 5]	5 [2, 9]	6 [3, 11]	0.53
Length of hospital stay (days, [IQR]))	17 [10, 35]	13 [7, 30]	17 [8, 28]	24 [6, 46]	0.24
Length of ICU stay (median [IQR])	8 [3, 16]	11 [3, 18]	8 [2, 18]	7 [2, 14]	0.23
In-hospital mortality (%)	12 (23)	11 (23)	21 (41)	18 (38)	0.26
GOSE 6-months (%)					0.53
1=Dead	18 (34)	14 (29)	21 (41)	20 (42)	
2=Vegetative state/3=Lower severe disability	15 (28)	13 (27)	11 (22)	6 (12)	
4=Upper severe disability	3 (6)	1 (2)	3 (6)	5 (10)	
5=Lower moderate disability	3 (6)	10 (21)	7 (14)	6 (12)	
6=Upper moderate disability	1 (2)	0 (0)	2 (4)	3 (6)	
7=Lower good recovery	6 (11)	7 (15)	4 (8)	6 (12)	
8=Upper good recovery	7 (13)	3 (6)	3 (6)	2 (4)	

Abbreviation: CPP, cerebral perfusion pressure; DC, decompressive craniectomy; GOSE, Glasgow Outcome Scale Extended; ICU, intensive care unit; IQR, interquartile range; SMD, standardized mean difference; TIL, therapy intensity level.

[a] Neuroworsening is defined as: a spontaneous decrease in the Glasgow Coma Scale motor score ≥ 2 points (compared with the previous examination), a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm, and/or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.

[b] Progression on the CT scan during the hospital course is defined as an increase in initial lesion and/or the development of a new lesion.



eFigure 1. Propensity scores distribution of nonmatched cohorts and propensity matched cohorts of primary decompressive craniectomy

The propensity of being exposed to the intervention was computed using multivariable logistic regression with primary decompressive craniectomy as the dependent variable. Propensity score matching was used to match exposed patients with non-exposed patients. The maximum difference between propensity scores was set at 0·10 (the caliper) using a nearest neighbor approach in 1:1 balance.

eTable 6. Results of sensitivity analyses: comparing analytical methods to adjust for confounding by indication in proportional odds logistic regression models with the Glasgow Outcome Scale Extended score as outcome

Approach	Primary DC (common OR 95 % CI, number of patients)
Unadjusted model	0.4 (0.3 – 0.6, n = 336)
Covariable adjustment [a]	0.4 (0.2 – 0.6, n = 336)
Propensity score matching [b]	0.4 (0.3 – 0.8, n = 174)
Instrumental variable [c]	
With the cohort with centers < 15 patients excluded	0.9 (0.5 – 1.5, n = 97)
Predefined instrument (in provider profiling) [d]	0.9 (0.4 – 2.2, n = 204) [d]

Abbreviation: CI, confidence interval; DC, decompressive craniectomy; OR, odds ratio.

[a] Model was adjusted for the following confounders: age, GCS, pupillary reactivity, midline shift, concomitant contusion and hematoma size, including a random intercept for center.

[b] A propensity score was calculated based on the following variables: age, GCS, pupillary reactivity, midline shift, concomitant contusion and hematoma size, including a random intercept for center.

[c] The adjusted common OR indicates the odds of a more favorable outcome for an increase of the 25th percentile to the 75th percentile of the range in exposure to the regional intervention preferences. In this random effects model, the random intercept for each center represents the unexplained center effect (beyond all factors included in the model, including the instrument treatment preference).

[d] Centers provided in a questionnaire - before patient enrolment - whether they employ a pre-emptive and/or routine approach with regard to DC when evacuating ASDH. For the current analysis, the threshold for primary DC surgery for ASDH was dichotomized accordingly: ''Yes', primary DC routinely/pre-emptively versus 'No', no primary DC routinely/pre-emptively were compared.

The association could not be estimated on the cohort with centers providing 15 patients, because there were no 'routing/pre-emptive centers'. Instead, the cohort with centers providing at least 10 patients were used.

eTable 7. Unadjusted patient-level analysis

Outcome	Patient-level analyses			
	Primary DC (n = 91)	Craniotomy (n = 245)	Effect variable	Unadjusted value (95% CI)
Primary outcome: GOSE at 6 months (median [IQR])	3 [1-4]	4 [1-6]	Common odds ratio	0.4 (0.3 – 0.6)
Secondary outcomes				
In-hospital mortality	35 (38)	58 (24)	Odds ratio	2.0 (1.2 – 3.4)
GOSE of 7 or 8 (%)	4 (4)	50 (20)	Odds ratio	0.2 (0.1 – 0.5)
GOSE of 5-8 (%)	18 (20)	108 (44)	Odds ratio	0.3 (0.2 – 0.6)
GOSE of 4-8 (%)	26 (29)	126 (51)	Odds ratio	0.4 (0.2 – 0.6)
QOLIBRI (median [IQR]) at 6 months [a]	69 (60-80)	76 (60-85)	Beta	-3.9 (-12.5 – 4.7)

Abbreviation: CI, confidence interval; DC, decompressive craniectomy; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; Na, not available; QOLIBRI, Quality of Life after Brain Injury Scale.

[a] QOLIBRI is a standardized health specific quality of life measure specifically designed for and validated in outcome assesment in patients with brain injury. It is a numerical scale with scores ranging from 0 to 100, with higher scores indicating a better quality of life. The score was avaiable for 19 patients of the primary DC group and 111 of the craniotomy group.

eTable 8. Baseline characteristics of propensity matched cohort, comparing primary decompressive craniectomy with craniotomy

Patient characteristic		Treatment status (n = 174)		
		Decompressive craniectomy	Craniotomy	SMD
n		87	87	
Age (median [IQR])		51 [36, 63]	47 [34, 59]	0.2
ASAPS (%)				0.4
Healthy		48 (55)	51 (59)	
Mild systemic disease		17 (20)	26 (30)	
Severe systemic disease		13 (15)	5 (6)	
Threat to life		1 (1)	1 (1)	
Unknown		8 (9)	4 (5)	
Hypoxia (%)				0.5
	No	65 (75)	68 (78)	
	Definite	13 (15)	3 (3)	
	Suspect	5 (6)	7 (8)	
	Unknown	4 (5)	9 (10)	
Hypotension (%)				0.3
	No	76 (87)	68 (78)	
	Definite	3 (3)	5 (6)	
	Suspect	3 (3)	5 (6)	
	Unknown	5 (6)	9 (10)	
Any major extracranial injury (%)		46 (53)	37 (43)	0.4
GCS (median [IQR])		5 [3, 8]	4 [3, 7]	0.2
GCS motor (median [IQR])		1 [1, 4]	1 [1, 4]	0
Pupils (%)				0.2
Both reacting		54 (62)	52 (60)	
One reacting		12 (14)	12 (14)	
Both unreacting		21 (24)	23 (26)	
CT large ASDH (%)		66 (76)	60 (69)	0
CT midline shift measure (mm)		8 [5, 13]	8 [4, 13]	0
CT contusion (%)				0.2
No		28 (32)	31 (36)	
Small		37 (43)	31 (36)	
Large		19 (22)	20 (23)	
Unknown		3 (3)	5 (6)	
GOSE (%)				0.5
1=Dead		36 (41)	23 (26)	
2=Vegetative state/3=Lower severe disability		26 (30)	23 (26)	

eTable 8. Baseline characteristics of propensity matched cohort, comparing primary decompressive craniectomy with craniotomy (*continued*)

Patient characteristic	Treatment status (n = 174)		
	Decompressive craniectomy	Craniotomy	SMD
4=Upper severe disability	8 (9)	8 (9)	
5=Lower moderate disability	12 (14)	15 (17)	
6=Upper moderate disability	1 (1)	6 (7)	
7=Lower good recovery	3 (3)	7 (8)	
8=Upper good recovery	1 (1)	5 (6)	

Abbreviation: ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; SMD, standardized mean difference.

eTable 9. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy, excluding centers < 15 patients

Patient characteristic	Treatment preference (observed primary DC rates per centre) [a]			
	Tertile 1 (0 – 22)	Tertile 2 (22 – 45)	Tertile 3 (45 – 67)	SMD
n	42	40	15	
Age (median [IQR])	62 [56, 68]	63 [41, 68]	44 [31, 58]	0.6
ASAPS (%)				0.8
Healthy	25 (60)	20 (50)	3 (20)	
Mild systemic disease	14 (33)	12 (30)	8 (53)	
Severe systemic disease	3 (7)	7 (18)	2 (13)	
Threat to life	0 (0)	1 (3)	0 (0)	
Unknown	0 (0)	0 (0)	2 (13)	
Hypoxia (%) [b]				0.8
No	30 (71)	35 (88)	11 (73)	
Definite	1 (2)	5 (13)	2 (13)	
Suspect	2 (5)	0 (0)	2 (13)	
Unknown	9 (21)	0 (0)	0 (0)	
Hypotension (%) [c]				0.6
No	32 (76)	38 (95)	13 (87)	
Definite	1 (2)	1 (3)	0 (0)	
Suspect	0 (0)	1 (3)	1 (7)	
Unknown	9 (21)	0 (0)	1 (7)	
Any major extracranial injury (%) [d]	20 (48)	20 (50)	8 (53)	0.1
GCS baseline (median [IQR])	8 [3, 11]	7 [3, 9]	5 [4, 13]	0.2
GCS motor baseline (median [IQR])	4 [1, 5]	1 [1, 5]	3 [2, 6]	0.4
Pupils (%)				0.5

eTable 9. Selected baseline characteristics and prognosis across centers with different preferences for primary decompressive craniectomy, excluding centers < 15 patients (*continued*)

Patient characteristic	Treatment preference (observed primary DC rates per centre) [a]			
	Tertile 1 (0 – 22)	Tertile 2 (22 – 45)	Tertile 3 (45 – 67)	SMD
Both reacting	28 (67)	23 (58)	9 (60)	
One reacting	3 (7)	7 (18)	0 (0)	
Both unreacting	11 (26)	10 (25)	6 (40)	
Total volume of ASDH (cm3, median [IQR])	61 [33, 97]	73 [33, 100]	47 [17, 79]	
CT large ASDH (%) [f]	29 (69)	34 (85)	10 (67)	0.3
CT midline shift (%) [e]	32 (76)	38 (95)	14 (93)	0.4
CT contusion (%)				0.5
No	14 (33)	16 (40)	3 (20)	
Small	20 (48)	20 (50)	10 (67)	
Large	8 (19)	3 (8)	2 (13)	
Unknown	0 (0)	1 (3)	0 (0)	
CT subarachnoid hemorrhage (%)				0.8
No	13 (31)	9 (23)	6 (40)	
Basal	5 (12)	2 (5)	0 (0)	
Cortical	17 (41)	25 (63)	3 (20)	
Basal and cortical	7 (17)	4 (10)	6 (40)	0.2
CT basal cisterns absent/compressed (%)	18 (43)	19 (48)	9 (60)	0.5
Mean predicted 6-month unfavorable outcome (GOS score ≤ 3, %, median [IQR]) [g]	76 [57, 88]	83 [64, 91]	65 [45, 73]	0.2

Abbreviation: AIS, Abbreviated Injury Scale; ASAPS, American Society of Anesthesiologists classification system; ASDH, acute subdural hematoma; DC, decompressive craniectomy; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale (5-point); IQR, interquartile range; IV, instrumental variable; SAH, subarachnoid hemorrhage

[a] Treatment preference as defined by the case-mix adjusted probability of undergoing acute surgery (as opposed to initial conservative treatment) based on the observed acute surgery rates per centre. This corresponds to the IV status and presented in quartiles of the range of adjusted regional primary DC rates. The first category is less aggressive than the second and the second is less aggressive than the third and so forth. Importantly, the IV analysis used the acute surgery rates as continuous preference, the quartiles are presented for purposes of interpretability of baseline comparability.

[b] Second insult during the pre-hospital or ER phase, defined as PaO2 < 8 kPa (60 mmHg)/SaO2 < 90%. 'Suspected' was scored if the patient did not have documented hypoxia by PaO2 or SaO2, but there was a clinical suspicion, as evidenced by for example cyanosis, apnoea or respiratory distress.

[c] Second insult during the pre-hospital or ER phase, defined as systolic BP < 90 mmHg. 'Suspected' was scored if the patient did not have a documented blood pressure, but was reported to be in shock or have an absent brachial pulse (not related to injury of the extremity)

[d] AIS □ 3

[e] Large is defined qualitatively by the treating neurosurgeon and corresponded to a size larger than 25 cm³.

[f] Midline shift present is classified as being more than 5 mm.

[g] TBI severity as summarized in predicted unfavorable outcome, proportion with a Glasgow Outcome Scale score ≤ 3, based on CRASH-CT variables

eTable 10. Hospital course and outcome across centers with different preferences for primary decompressive craniectomy, excluding centers < 15 patients

	Treatment preference (observed primary DC rates per centre)			
	Tertile 1 (0 – 22)	**Tertile 2 (22 – 45)**	**Tertile 3 (45 – 67)**	**SMD**
n	42	40	15	
Length of hospital stay (median [IQR])	21 [10, 35]	17 [8, 25]	41 [21, 66]	0.3
Length of ICU stay (median [IQR])	12 [6, 18]	9 [2, 17]	10 [5, 18]	0.1
ICP monitor (%)	36 (86)	25 (62)	12 (80)	0.4
ICP (median [IQR])	12 [9, 17]	12 [7, 19]	12 [10, 16]	0.1
Any neuroworsening (%) [a]	17 (40)	21 (52)	10 (67)	0.4
Progression on CT (%) [b]	19 (45)	18 (45)	7 (47)	<0.1
In-hospital mortality (%)	11(26)	16 (40)	4 (27)	0.2
GOSE (%)				0.8
1=Dead	16 (38)	17 (42)	5 (33)	
2=Vegetative state/3=Lower severe disability	11 (26)	10 (25)	3 (20)	
4=Upper severe disability	3 (7)	1 (3)	3 (20)	
5=Lower moderate disability	2 (5)	5 (13)	3 (20)	
6=Upper moderate disability	1 (2)	1 (3)	1 (7)	
7=Lower good recovery	5 (12)	4 (10)	0 (0)	
8=Upper good recovery	4 (10)	2 (5)	0 (0)	

Abbreviation: DC, decompressive craniectomy; GOSE, Glasgow Outcome Scale Extended; ICU, intensive care unit; IQR, interquartile range

[a] Neuroworsening is defined as: a spontaneous decrease in the Glasgow Coma Scale motor score ≥ 2 points (compared with the previous examination), a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm, and/or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.

[b] Progression on the CT scan during the hospital course is defined as an increase in initial lesion and/or the development of a new lesion.

eTable 11. Primary and secondary outcomes and treatment associations for primary decompressive craniectomy, excluding centers < 15 patients

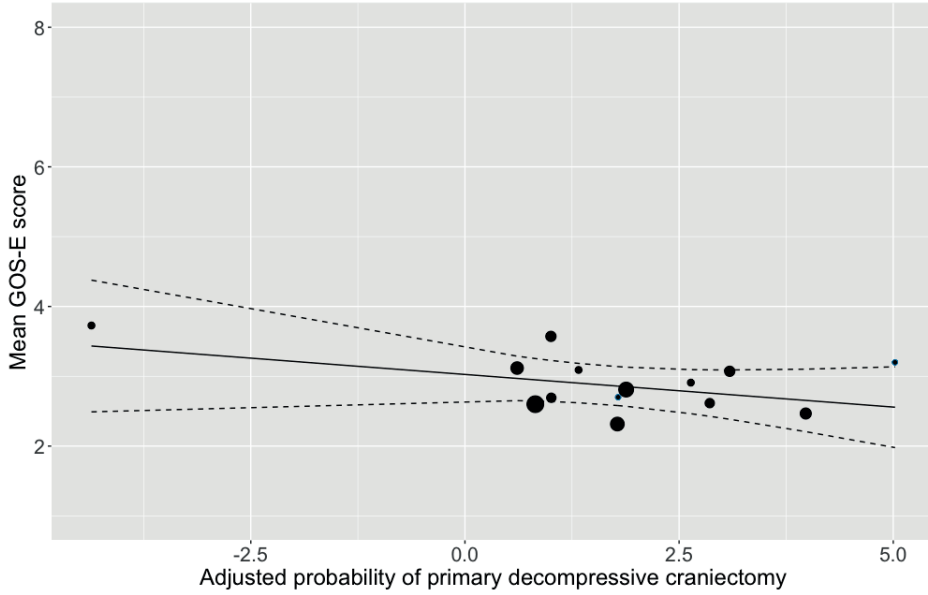
Outcome	*Intervention (n = 91)*	*Control (n = 245)*	*Effect parameter*	*Unadjusted value of patient-level analysis (95% CI, n = 336)*	*Adjusted value of center-level analysis (95% CI, n = 97)* [a]
Primary outcome: GOSE at 6 months (median [IQR])	3 [1-4]	4 [1-6]	Common odds ratio	0.4 (0.3 – 0.6)	0.9 (0.5 – 1.5)
Secondary outcomes					
In-hospital mortality	35 (38)	58 (24)	Odds ratio	2.0 (1.2 – 3.4)	1.0 (0.5 – 2.4)
GOSE of 7 or 8 (%)	4 (4)	50 (20)	Odds ratio	0.2 (0.1 – 0.5)	0.5 (0.2 – 1.2)
GOSE of 5-8 (%)	18 (20)	108 (44)	Odds ratio	0.3 (0.2 – 0.6)	1.0 (0.5 – 1.8)
GOSE of 4-8 (%)	26 (29)	126 (51)	Odds ratio	0.4 (0.2 – 0.6)	1.2 (0.5 – 1.7)
QOLIBRI (median [IQR]) at 6 months [b]	69 (60-80)	76 (60-85)	Beta	-3.9 (-12.5 – 4.7)	Na [c]

Abbreviation: CI, confidence interval; GOSE, Glasgow Outcome Scale Extended; IQR, interquartile range; IV, instrumental variable; Na, not available; QOLIBRI, Quality of Life after Brain Injury Scale.

[a] IV analysis with estimates with from random effect multivariable ordinal regression with the instrument, adjusted probability of undergoing primary DC as treatment variable. Confounding was furthermore addressed by adjusting for the a-priori defined variables age, GCS, pupil reactivity, hematoma size, contusion presence and midline shift. The adjusted common OR indicates the odds of a more favorable outcome for an increase of the 25th percentile to the 75th percentile (IQR) of the range in exposure to the center intervention preferences.

[b] QOLIBRI is a standardized health specific quality of life measure specifically designed for and validated in outcome assesment in patients with brain injury. It is a numerical scale with scores ranging from 0 to 100, with higher scores indicating a better quality of life. The score was avaiable for 19 patients of the primary DC group and 111 of the craniotomy group.

[c] The association estimate could not be estimated due to low numbers (no centers with more than 15 patients in the subcohort).



eFigure 2. Functional outcome of centers with different probabilities of primary decompressive craniectomy

Graphical illustration to estimate the incremental effect of more primary decompressive craniectomy. Each circle represents a center with the area being proportional to the number of patients per center. The fitted line is the result of an adjusted random effects linear model with dotted lines reporting the 95% confidence intervals. The mean GOSE decreased non-significantly with 0.1 for primary DC (95% CI: -0.2 – 0.1, n = 200).

REFERENCES

1. Stukel TA, Fisher ES, Wennberg DE, et al. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007;297(3):278-285.
2. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiol Drug Saf* 2010;19(6):537-554.
3. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clin Epidemiol* 2018;10:841-852.
4. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363-369.
5. Van Essen TA, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe. *BMJ Open* 2019;9(10):e033513.
6. van Essen TA, den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir (Wien)* 2019;161(3):435-449.

PART V

GENERAL DISCUSSION

Chapter 13

Summary

SUMMARY

In **Chapter 1**, the knowledge on the surgical management of the acute subdural hematoma (ASDH) in traumatic brain injury (TBI) is summarized. The ASDH is the most prevalent TBI and evacuation of an ASDH is one of the most common acute neurosurgical intervention.[1] Neurosurgeons in favor of evacuation of a subdural estimate that acting too slowly or not at all when there is a large ASDH leads to neurological deterioration or death. Their suspicion is backed by the Brain Trauma Foundation (BTF) guideline, which was devised in 2005 by an international panel of experts and states that every ASDH with a thickness >10mm and a midline shift over 5mm and every ICH larger than 50 cm^3 should be evacuated, irrespective of neurological condition.[2,3] On the other hand, surgeons in favor of a conservative strategy do not want to expose the patient to the risks of a craniotomy or decompressive craniectomy (DC) without a more precise estimation of the chance of neurological deterioration when withholding an operation. It can be argued that the guideline and the evidence so far should not guide treatment, because good quality comparative studies are lacking.

The lack of sound evidence to guide this decision in TBI was the motivation for this PhD project. Subsequently, we postulated the research questions:

I. What is the current evidence on the effectiveness of surgical treatment of ASDH?
II. What is the current practice in treatment of patients with ASDH in Europe?
III. Which study designs and analyses are suited to determine the effectiveness of surgical treatment of ASDH?
IV. What is the effectiveness of different treatment approaches (surgery versus initial conservative Treatment, and DC versus craniotomy) for ASDH?

Thereafter, we described the datasets of Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) cohort and the Neurotraumatology Quality Registry (Net-QuRe) that we used to answer the questions.

In **PART I** the current evidence is updated. The summary in **Chapter 2** gives an overview of current comparative studies in surgical TBI and opportunities for future research. **Chapter 3** is a systematic review on the effect of surgery in ASDH. We try to improve the current evidence base by using already performed studies. In the first systematic review of the mortality risk in ASDH, we included 102 studies comprising 12,287 patients. The overall mortality in surgically treated ASDH was 48% (95% confidence interval [CI] 44-53%) while mortality was 41% (95% CI 31-51%) in comatose ASDH patients that were surgically treated. The mortality risk associated with the conservative treatment of comatose ASDH patients was 81%

(95% CI 56-98%). In a dramatic effect design, we show that the size of the beneficial effect of surgical evacuation equals 40% mortality reduction.

In **PART II** we describe the current neurosurgical management strategies of TBI. The first study, **Chapter 4**, is a survey in The Netherlands and Belgium on how patients with ASDH are managed. The research question is whether the varying trauma management of ASDH is the result of a variable view among neurosurgeons. Regular day-to-day cases of TBI and an ASDH were presented to them online. Sixty neurosurgeons filled out the questionnaire (response rate 65%). For patients with severe TBI and ASDH (three cases) there was a modest variation in the decision to surgically evacuate the hematoma or not; respectively 88%, 100%, and 77% would perform acute surgery. The variation became more pronounced for patients with a moderate or mild TBI. For example, in a hypothetical case of a 79-year-old male with a mild TBI and a fairly large ASDH, 1 out of 7 (14%) neurosurgeons in one region chose a surgical strategy compared with 9 out of 10 (90%) in another region for the same scenario. However, despite this distinct practice variation, less than half of (the same) neurosurgeons (48%) would leave this decision open for randomization in a study. This practice variation together with the fact that this group, mild or moderate TBI and ASDH, represents the majority of patients with an ASDH, were the impetus for our further research. The variation supports the methodology of the international Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) initiative, and shaped the Dutch Neurotraumatology Quality Registry (Net-QuRe) initiative.[4,5]

This overview of contemporary neurosurgical care in The Netherlands and Belgium is complemented in **Chapter 5**, by a survey aimed to explore differences in neurosurgical strategies for TBI across Europe. The questionnaire consisted of several topics among which the decision when to operate (or not) on traumatic ASDH and ICH, and when to perform a decompressive craniectomy (DC) in raised intracranial pressure (ICP). The survey was completed by 68 centers (100%), mostly by neurosurgeons (78%). All centers provide 24/7 acute neurosurgical coverage, at least within 30 minutes. ASDH represents the highest volume of neurosurgical TBI cases, on average 25 cases per year (per center). Forty percent of responders reported a thickness or volume threshold for evacuation of an ASDH. Most responders (78%) decide on a primary DC in evacuating an ASDH during the operation, when swelling is present. For ICH, 3% would perform an evacuation directly, i.e. on presentation, to prevent secondary deterioration and 66% only in case of clinical deterioration. Treatment strategies varied substantially between regions, specifically for the threshold for ASDH surgery and DC for refractory raised ICP. 31% of centers reported variation within the hospital for inserting an ICP monitor and 43% for evacuating

mass lesions. The results of the questionnaire point out potential substrates for comparative effectiveness research (CER) in CENTER-TBI.

In **PART III** deals with the preparation of designing our study, methodological choices made, to meet our effectiveness objectives. Specifically, it describes two case studies, a review of the literature concerning how to design an observational study to determine the effectiveness of acute intracranial interventions, and the protocol for the main comparative effectiveness studies.
Observational studies constitute the alternative to the gold-standard of a randomized controlled trial (RCT). A key challenge in observational studies of interventions is confounding by indication, a phrase that refers to a situation where patient characteristics, rather than the intervention, are independent predictors of outcome. The objective of the study in **Chapter 6** was to define the circumstances for the validity of methods to adjust for confounding in observational studies of interventions in TBI. Three large TBI datasets were used to perform post-hoc analyses with the interventions intracranial pressure (ICP) monitoring, intracranial operation and primary referral. Multivariable regression, propensity score matching and instrumental variable (IV) analysis were compared. Furthermore, in a simulation study these methods were compared in their ability to correct unmeasured confounding in a hypothetical not further defined intervention. For all three interventions, multivariable regression and propensity score matching resulted in negative estimates of the treatment effect (OR ranging from 0.80 to 0.92), whereas the IV approach indicated that both ICP monitoring and intracranial operation might be beneficial (OR per 10% change 1.17, 95% CI 1.01–1.42 and 1.42, 95% CI 0.95–1.97). In our simulation study, multivariable regression and propensity score matching resulted in an invalid estimate of the treatment effect in case of unmeasured confounders (OR ranging from 0.90 to 1.03). The IV approach provided an estimate in the similar direction as the simulated effect (OR per 10% change 1.04–1.05) but was statistically inefficient. The conclusion is that IV analysis might provide a more valid estimate of the treatment effect compared to conventional analytical methods. However, the findings also suggest that alternative methods should be used simultaneously to strengthen the credibility of effect estimation.[6]
Chapter 7 is a letter to the editor in which we respond to an observational study investigating the effect of surgical evacuation for spontaneous intracerebellar hematoma.[7]We question the validity of the results and we point out our concerns with regards to the study analysis. We suggest that the study should preferably use an IV effect estimation to reliably correct for the unmeasured confounding because the cohort stems from 64 centers with likely differing practice culture. In their response the authors performed this analysis and conclude to have provided similar

results as with their original estimates across the investigated primary and secondary outcomes.[8]

In **Chapter 8**, we work out a proposal for the comparative studies. We designed part of the CENTER-TBI cohort and setup the Net-QuRe with the aim to answer who to surgically treat acutely in ASDH, ICH and when to perform a primary DC. This study uses a comparative effectiveness research (CER) design, a multicenter prospective observational cohort study that exploits variation in neurotrauma care to create and compare parallel study groups. The multicenter design is necessary to ensure the required number of patients with different neurotrauma treatment strategies for ASDH and t-ICH. Patients with an ASDH and/or a t-ICH are eligible for inclusion. Inherent to the observational design of this study the management strategies under investigation proceed according to local emergency and intensive care protocols or surgeon's expertise. Consequently, the resulting variation in management is accepted and analyzed. To gain insight into this variation, detailed information is collected on the reasons for specific interventions or management strategies (see section 'why' questions). The interventions of interest are acute surgery, defined as surgery directly after the first CT at presentation versus late or no surgery and craniotomy versus DC. The primary outcome measure is the Glasgow Outcome Score-Extended at 6 months. Secondary outcome measures include in-hospital mortality, quality of life and neuropsychological tests. In the primary analysis, the effect of treatment preference (i.e. the proportion of patients in which the intervention under study is preferred) per hospital will be analyzed with random effects proportional odds ordinal regression models, adjusted for case mix. Sensitivity analyses will include (conventional) multivariable regression modelling and propensity score matching, with treatment defined on patient level. In CENTER-TBI and Net-QuRe together approximately 1000 patients with ASDH and 750 patients with ICH were expected, recruited from approximately 70 centers. These samples would lead to a power of 80% to detect a difference (assuming a two-sided significance 0.05).

PART IV is focused on the effectiveness of surgery in ASDH. Timely evacuation of an expanding traumatic intracranial hematoma in a patient with deteriorating level of consciousness is lifesaving. Most patients with a traumatic intracranial hematoma, however, present with a moderately decreased or high conscious level. Uncertainty exists, particularly in patients with an ASDH or an ICH on indications, timing of surgery and type of surgery, reflected in large practice variations.

We start with an observational comparative effectiveness study among two trauma regions in The Netherlands in **Chapter 9**. We compared treatment strategies on center level rather than patient level to reduce confounding by indication. These regions are geographically distinct and covered by separate neurosurgical departments. These

regions were chosen for their – a-priori defined – diverging treatment preferences derived from the survey in Chapter 7. Baseline characteristics were comparable between regions. The median age was relatively high at 68 years (interquartile range [IQR], 54–76). Primary evacuation was performed in 84% of patients in region A and in 65% of patients in region B ($p < 0.01$). The strategy favoring surgical evacuation was associated with significantly lower odds of unfavorable outcome (OR 0.53; 95% CI: 0.27–1.02) 3–9 months post-injury. Thus, we concluded that an aggressive surgical management strategy might be associated with better outcome in an elderly population with traumatic ASDHs. However, the important limitation is that other regional differences might account for this finding. The higher incidence of clinical deterioration in one of these regions, for example, may be consequent to the larger number of secondary referrals. Primary presentation to a neurosurgical center has a close relationship with time to surgery and could even improve patient outcome.[9] And although the primary referral and other imbalances are counteracted by other (measured) confounders – after all, the cohorts of both regions have a similar prognosis according to a validated prognostic model - residual confounding is possible. We proposed larger comparative studies with more hospitals to examine this effect of surgery and to explore generalizability (**Chapter 8**).

In **Chapter 10** we analyzed data on 1407 patients with an ASDH and found that the proportion of patients undergoing acute surgery ranged from 6 to 52% (interquartile range [IQR] = 13-35%) between centers. The resulting median odds ratio (MOR) of 1.8 ($p < 0{\cdot}001$) can be interpreted as a twofold higher probability that an identical patient will receive acute surgery in one versus another random center. These large between-center variations enabled exploration of effectiveness of surgery in comparative effectiveness analyses. For acute surgery in ASDH, we found that center preference for an acute surgical strategy over that of an (initial) conservative treatment was not significantly associated with better outcome (odds ratio 0.92 [95% CI 0.77 to 1.09]). Delayed surgery within the conservative group (n=982) occurred in 107 patients (11%) after a median of 19.1 hours (IQR 8.1-84.6). These results should be interpreted in light of the comparative effectiveness design and do not imply no effect of surgery. Because an identical patient may be operated in one center but not in another, it naturally follows that there is more than one valid treatment option. The results apply to those patients for whom the neurosurgeon sees no clear superiority of either treatment. Therefore, the data suggest that acute surgical evacuation of an ASDH in patients for whom equipoise exists on surgical indication may not lead to a better outcome compared to (initial) conservative treatment.
In **Chapter 11** we respond to a letter to the editor in which some aspects of our study in Chapter 10 are questioned.[10]

In **Chapter 12**, we explored the effectiveness of a primary DC as compared to a craniotomy in patients with ASDH, by exploiting the aforementioned practice variation. The type of primary acute surgery for ASDH highly varied between centers: the proportion of patients undergoing primary DC of all acute surgeries, as opposed to craniotomy ranged from 6 to 67 % (IQR = 12-26%) with an adjusted MOR for primary DC of 2.7 ($p < 0 \cdot 001$). Centre preference for primary DC over craniotomy to evacuate the hematoma was not associated with a better outcome (odds ratio per 13% (IQR) more primary DC in a center 1.09 [95% CI 0.53 to 1.53]). Again, these findings apply to those patients for which there is uncertainty in the first place. We conclude that the initial decision for primary DC should be restricted to those salvageable patients for which craniotomy is not a reasonable alternative. The decision for primary craniotomy leads to similar outcome, has less complications and does not need a cranioplasty to achieve this outcome.

The decision whether to operate or not in patients with a traumatic ASDH can, in many cases, be a neurosurgical dilemma. In the current thesis the surgical treatment of TBI was studied and discussed. Current treatment strategies were described, clinical characteristics of the patient domain were studied and the optimal study methodology to answer the effectiveness questions was examined. This thesis contributes to the assessment of surgical interventions in TBI and will influence future research.

REFERENCES

1. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–92.
2. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006;58(3 Suppl):S16–24–discussionSi–iv.
3. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006;58(3 Suppl):S25–46–discussionSi–iv.
4. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76(1):67–80.
5. Nederlands Trial Register [Internet]. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.
6. Laborde-Castérot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. *Journal of Clinical Epidemiology* 2015;68(10):1232–40.
7. Kuramatsu JB, Biffi A, Gerner ST, et al. Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage. *JAMA* 2019;322(14):1392–12.
8. Kuramatsu JB, Sheth KN, Huttner HB. Unmeasured Confounding in Observational Studies of Management of Cerebellar Intracranial Hemorrhage-Reply. *JAMA* 2020;323(7):666.
9. Stone JL, Lowe RJ, Jonasson O, et al. Acute subdural hematoma: direct admission to a trauma center yields improved results. *The Journal of Trauma: Injury, Infection, and Critical Care* 1986;26(5):445–50.
10. Beucler N. Treatment of acute subdural haematoma. *The Lancet Neurology* 2022;21(12):1080.

Chapter 14

Discussion

DISCUSSION

The overall aim of this thesis was to evaluate the effectiveness of surgical treatment approaches for patients with traumatic acute subdural hematoma (ASDH). The main research questions were:

I. What is the current evidence on the effectiveness of surgical treatment of ASDH?
II. What is the current practice in treatment of patients with ASDH in Europe?
III. Which study designs and analyses are suited to determine the effectiveness of surgical treatment of ASDH?
IV. What is the effectiveness of different treatment approaches (surgery versus initial conservative treatment and decompressive craniectomy versus craniotomy) for ASDH?

In this chapter I first discuss the key findings of the thesis. Thereafter, I reflect on the key findings, critically appraise surgical intervention research using observational data, and discuss limitations. Finally, I propose recommendations for clinical practice and future research.

Key findings

I first studied the **current evidence** (Part I) of surgery for ASDH in a systematic review. Available literature was limited to observational cohorts or case series, with selected populations, mostly performed more than two decades ago. There were no comparative studies. In a meta-analysis comparing contemporary surgical prognosis with historical conservative prognosis I concluded a strong effect of surgery in comatose patients.

Surveys of **current practice** (Part II) showed large practice variation with regard to whether to operate or not in ASDH. In addition, the willingness among neurosurgeons to randomize to surgery or conservative treatment was low.

In Part III we studied the methodological **challenges of studying acute neurosurgical interventions** using observational data. I evaluated which analysis strategy would be best suited to minimize the confounding in studies on acute neurosurgical interventions. Instrumental variable (IV) analysis might provide a more valid estimate of the treatment effect compared to conventional analytical methods. The methodological justification of this design and the data collection and the analysis were documented in a protocol for the actual effectiveness study.

In Part IV I determined **the effectiveness of neurosurgical interventions in acute subdural hematoma**. In a retrospective comparative effectiveness study comparing treatment preferences of two centers, I concluded that a treatment strategy favoring emergency hematoma evacuation might be associated with better outcome. However, residual confounding might explain the results and, therefore, larger,

prospective, comparative studies with more hospitals were needed. I then performed a prospective comparative effectiveness study that showed that similar patients with ASDH were indeed treated differently due to varying treatment preferences. A treatment strategy preferring an aggressive approach of acute surgical evacuation over initial conservative treatment was not associated with better outcome. Finally, I showed that a primary decompressive craniectomy (DC) does not seem to lead to a better outcome than ASDH evacuation by craniotomy although the results are uncertain due to a small sample.

Reflection on key findings

The thesis is the result of a stepwise, tinkering process in trying to find ways to determine the effectiveness of a longstanding surgical intervention, acute surgery for ASDH, that is considered well-established among the expert community. I have critically appraised the proof of concept (IDEAL framework stage 1) by developing and exploring methods (IDEAL stage 2) to asses and falsify the supposed benefit of acute surgery (IDEAL stage 3).

Especially as neurosurgeons, we know that acute surgery in ASDH can be highly effective in specific cases. My first study came about in my wish to integrate this neurosurgical common sense with evidence-based medicine. I presented the first published systematic review of ASDH surgery. Despite the lack of comparative studies, I could reliably demonstrate that surgical evacuation of ASDH greatly reduces mortality risk in comatose patients (**Chapter 3**). The methodology stems from a paper using meta-analysis with 'dramatic effect' methodology to deduce the effectiveness of a parachute.[11] This methodology resonated with us because the comparison of research in ASDH surgery to a parachute in skydiving had often been made.[2]

This study also highlights the improved care for patients with severe TBI and ASDH over the past century in modern well-resourced hospitals.[3] Targeted and efficient neurosurgery, advances in neurocritical care and the widespread introduction of CT-scanners and ICP monitors have decreased mortality in severe TBI dramatically.[4] Most cases of ASDH, however, do not present in comatose state and most cases are not treated surgically (Table 1).

In **Chapter 3** I conclude that the current evidence base has not improved since the publication of the widely known Brain Trauma Foundation (BTF) guideline in 2006. 'To operate or not' therefore remains a decision surrounded with uncertainty. In **Chapter 2** I, therefore, have tried to move the needle among the scientific community and policy makers from the focus on descriptive small studies, reporting on prognosis of either treatment arm, to well-designed comparative effectiveness studies that aim to answer the actual relevant intervention question.

Subgroup	Number who had surgery/total number
Age	
<65 years	202/725
≥65 years	90/435
TBI severity	
Mild TBI	62/542
Moderate TBI	58/193
Severe TBI	172/425
Haematoma size	
Large	221/309
Small	71/851
Total	**292/1160**

Table 1. Proportion patients surgically treated of the CENTER-TBI cohort of patients with acute subdural hematoma, stratified for specific subgroups

The surveys (**Chapter 4 and 5**) showed large variation for treatment strategies in TBI, specifically for everyday ASDH cases (Figure 1). Although the regional variation in surgical treatment of ASDH has not been shown in the literature, other studies have shown that variability in treatment of TBI exists.[5,6] Moreover, in only 17% of a random sample of (brain) trauma patients care delivered according to the BTF guidelines, suggesting a variable approach.[7] In addition, there exists a difference in point of view among neurosurgeons with respect to combining the evacuation of an ASDH with a DC.[8]

The existing variation might be a sign of unwarranted care differences, but also a reflection of real-life neurosurgical practice in TBI. Decisions are made under large uncertainty, constrained not only by limited evidence, but also by time, in an emotionally charged environment, at moments when regular consultation with colleagues is difficult. Furthermore, clinicians need to make accurate prognostic estimates to inform surgical decision-making but this process is at best unequivocal.[9] What makes matters worse is that there seems to be a seemingly reasonable quality of life after severe TBI, which might be attributed to the disability paradox.[10]

Subsequently, I explored whether an RCT, the superior methodological approach for causal inference in clinical epidemiology,[11] would be possible. Unfortunately, the survey showed not enough willingness among neurosurgeons to randomize patients with an ASDH. Thus, I concluded that there is at present not sufficient clinical equipoise while, at the same time, opposite treatment strategies for similar patients are employed. An explanation for this contradiction might be that neurosurgeons extent the clear role of surgery in specific cases of ASDH to other - more uncertain

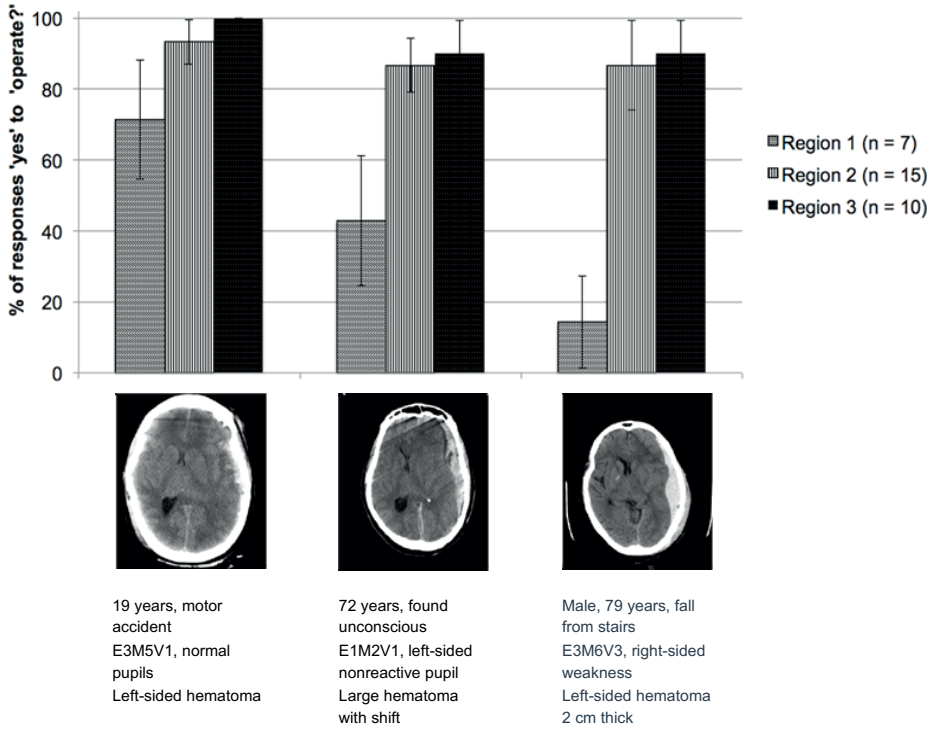


Figure 1. Regional variation with respect to operate or not in ASDH
Bar graph with percentages 'yes'-answers to the question whether surgery is indicated for these hypothetical clinical cases, stratified in three regions. Adapted from published paper in Chapter 4 and presented at the '11th Symposium of the International Neurotrauma Society' in Budapest, Hungary, march 2014.

- cases. Another explanation might be that this absence of clinical equipoise among the neurosurgical community implies a practice sometimes justified by the unique nature of surgery, an idea referred to as (neuro)surgical exceptionalism, which renders commonly used research methods from other medical disciplines unsuitable.[12] Anyway, starting an RCT would clearly not have been worthwhile, at least at the time in 2016.

Instead, I explored study designs that could reach the same level of validity. The idea was to setup a study that was specifically designed to exploit the existing variation. The resulting natural experiment mimics the counterfactual ideal of an RCT.[13,14] The methodological framework is called an IV analysis. This method originates from econometrics. An IV is a variable that is correlated to the treatment, but not to outcome. My hypothesis was that regional treatment preference is a valid IV.

In **Chapter 6**, we estimated, that, given the non-randomized data, an IV analysis is the superior approach because of its ability to account for unmeasured confounding but needs relatively large sample sizes to obtain reliable estimates. In addition, I

concluded that alternative methods should be used simultaneously to strengthen the credibility of effect estimation. Both conclusions are in line with an abundance of literature in other fields.[13,15-17]

In **Chapter 7** I suggested this approach in a letter to the authors of an observational study investigating the effect of surgical evacuation for another – but related – condition, the spontaneous intracerebellar hematoma.[18] Intracerebellar hematoma is pathophysiologically and anatomically different but the decision whether to operate or not represents a similar decision leading to similar considerations regarding potential study designs. I felt that the findings, based on propensity score matching, might be spurious due to (unmeasured) confounding. Instead I proposed a center-preference based IV because the cohort stemmed from 64 centers, with likely differing practice culture among institutions. In their response the authors indicated that they performed this analysis and that it led to similar results as with their original method.[19] They showed a considerable increase of the point estimate, albeit with a large confidence interval (including 1; no effect). Therefore, I contest their conclusion that the new IV analysis supports the robustness of the analysis. Instead, I suggest that it might point to an overall beneficial effect for early surgery.

After this intermezzo on intracerebellar hematoma I shift the focus back to traumatic ASDH. I collected data in the centers with the most divergent treatment preference from our national survey (region 1 and 3 in Figure 1) to compare patient characteristics, treatments and outcomes between them (**Chapter 9**). I show that indeed the strategy of regional data collection and analyses resulted in a comparable baseline prognosis. Despite this comparability, patients were more likely to be operated in the center a-priori preferring acute surgery. It appeared that the region preferring surgery actually had a better outcome. However, the small sample, residual confounding on center level with differences in referral patterns, and the inability to sufficiently take immortal time bias into account were major limitations.[20] Further, generalization to clinic should take into account the relatively high age of 68 (median). So, we would need larger cohorts with more detailed data collection that allowed for more rigorous adjustment and extrapolation.

The preceding studies shaped the methodology of my studies performed in the international Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, and the Dutch Neurotraumatology Quality Registry (Net-QuRe) initiative.[21,22] In the protocol I described the methodological choices (**Chapter 8**). Specifically, immortal time bias has been addressed through the design, in which I defined treatment groups after the first CT scan (showing the acute subdural hematoma), thereby aligning the start of the follow-up with treatment assignment. As a primary analysis an IV analysis was chosen to account for the confounding by indication.

The thesis culminates in the comparative effectiveness study (**Chapter 10**). The widely differing surgical practices coming from centers that on average treat similar patients enabled exploration of effectiveness of the immediate treatment strategies in IV analysis. I showed that for most patients with an ASDH conservative treatment is preferable. This conclusion has gone through ample evaluation to verify the assumptions but challenged the neurosurgical status quo.[40,41] In **Chapter 11**, an 'author's reply' to a letter to the editor, I respond to some of these opposing arguments, discuss concerns that might have arisen among neurosurgeons globally and emphasize the results of our effectiveness study of acute surgery in ASDH. I will further discuss the validity and generalizability in the next section of this discussion. Uncertainty also exists on the benefits of a DC, a procedure that aims to mitigate effects of raised intracranial pressure by removing part of the skull. DC is frequently performed in combination with the evacuation of focal lesions, but is associated with severe complications and its additional benefits are only mechanistically clear. DC can be performed as primary procedure (combined with evacuation of a hematoma) or as secondary procedure (to decompress the brain). In Europe and Australia, inferred from the CENTER-TBI and the harmonized Australian OzENTER cohort studies, DC was performed in 320 patients, and in most conducted as primary procedure (258/320; 81%).[23] In other parts of the world, DC is performed even more frequently: In the China CENTER-TBI registry, DC was performed in 48% of patients with severe TBI (1354/2804), mostly as a primary procedure.[24] Previous trials have investigated the effectiveness of DC as secondary procedure, but until recently no evidence was available to support the use of DC as primary procedure. The advantage of a DC is that it more effectively controls ICP elevation, which could lead to secondary brain injury and poor clinical outcome. However, DC necessitates an additional operation (cranioplasty) to reconstruct the cranium and the associated risk of complications such as infection, cerebral edema and bone-flap reabsorption.[25] Literature on the effect of primary DC versus craniotomy to treat ASDH is inconsistent, with mostly worse outcomes for primary DC.[1,3,6,7,21] In a similar analysis as our preceding study on acute surgery vs conservative treatment in ASDH, I showed that there is no difference in outcome between a primary DC vs craniotomy. Hence, a craniotomy, a less invasive procedure, is preferred (**Chapter 12**). An important limitation is the small sample size of the study (although still the largest to date), resulting in a wide confidence interval possibly obscuring a clinically relevant effect.

Challenges around analysis and interpretation of observational studies on acute neurosurgery

In the process of interpreting, reporting and publishing the results of our main effectiveness study (Chapter 10), extensive discussions took place regarding

the (causal) interpretation. I have adhered to several guidelines for the conduct and reporting of IV analysis (Table 2),[13,15,26,27] but these discussions highlight the challenges in disseminating results from non-randomized interventions studies

Confounding

An IV analysis is preferable in a setting were strong confounding is expected because of its ability to control for unmeasured confounding. I performed preparatory methodological studies and showed the same holds true for our case study of acute neurosurgical decisions in TBI.[28,29] However, IV also relies on strong assumptions itself, which are not always met. Our IV, surgery treatment rate as a proxy for surgeon's preference, fulfils these assumptions; the centers' treatment preference predicts the likelihood to get acute surgery and the preference does not have an effect on outcome other than through surgery (Chapter 7 and 10).[30,31] Furthermore, I found similar effects in propensity score matching and multivariable regression adjustment. The consensus is when multiple methods give similar results, like in our study, it tends to strengthen the credibility of the findings. It may be argued that confounding is fully controlled.[16,17]

An instrumental variable is a variable in nonexperimental data that can be thought to mimic the coin toss in a randomized trial.
If an appropriate and valid instrument is found, then the effects of measured and unmeasured confounding can be mitigated.
An IV analysis always has an experimental analog, however absurd the experiment sounds. The IV analysis is therefore based on "a natural experiment."
Assumption (1): The IV must predict treatment but that prediction does not have to be perfect. An IV that does a poor job of prediction is said to be weak.
Assumption (2): A valid IV will not be directly related to outcome, except through the effect of the treatment.
Assumption (3): A valid IV will also not be related to outcome through either measured or unmeasured paths.
In a randomized trial, the assumptions are met by design in the act of randomization. In an IV analysis, these assumptions must be empirically checked to the extent possible or assumed based on context and subject matter knowledge.
In cases of treatment-effect homogeneity, IV studies estimate the effect on the marginal subject, the average treatment effect for patients whose treatment was determined by the instrument

Abbreviation: IV, instrumental variable.

Table 2. Key points about instrumental variable analysis
Adapted from [13]

However, the analysis through center-specific surgery rates might have induced new confounding on center level. The question is whether the effect of specific neurosurgical treatment choices/policies on outcome can be based on between-center variation without being residually confounded by other associated center characteristics. Unfortunately, I cannot exclude that other (unmeasured) regional differences might have distorted the findings,[13] but I tried to make reasonable that this confounding is minimal. I have accounted for these center differences through various ways. The primary analysis, with the IV as treatment variable and GOSE as dependent outcome variable in regression modelling, also included a random effects term for center, thereby adjusting for center clustering of other care processes or hospital structures. These random-effects accounts for other between-center differences than the factors included in the model. I calculated the post-hoc intraclass correlation coefficient (ICC) to be 0.018, so around 2% of the variance in outcome is explained by center. This confirms the small contribution of other center differences than acute surgery to outcome. Furthermore, another CENTER-TBI study showed that specific treatment choices did not correlate with other treatment choices within the centers.[32] This is in line with what would be expected, because treatment decisions are made by different medical specialties.

Monotonicity

Center preference relates to the policy in a specific center, e.g. a more aggressive or a more conservative approach to surgical indications. The decision in individual patients is primarily based on patient symptomatology, but is of course influenced by the centers' treatment preference. As mentioned, an IV analysis relies on strong assumptions. One of these is whether the center preference is actually employed in the cohort in which we estimate the treatment effect. There can be a discrepancy between the center preference and what treatment is actually initiated. In RCT terms, what is the compliance to the center policy?

This is a relevant methodological assumption in IV analysis, commonly referred to as the monotonicity assumption.[31] Monotonicity in our case refers to consequent decision-making of the neurosurgeon: a patient treated by a neurosurgeon that prefers acute surgery, 'should' predominantly treat with acute surgery. When patients do not 'comply' to the surgeon's preference or the preference is not consequently employed, the monotonicity assumption does not hold. In other words, true monotonicity requires an absence of defiers. To determine the possible discrepancy of the center preference versus the actual individual patient decision we need to know whether a patient has been treated according to the preference of the surgeon (or the center). However, surgeon's preference is not measured per patient, and, even more elusive, preference in itself might not be measurable. In an RCT it is clear when a study

patient did not receive the treatment that was determined by the randomization. Thus, the monotonicity assumption in an IV analysis cannot be tested and is normally not empirically verified.[26]

However, I tried to examine this assumption in our study. We compared predefined preferences towards immediate ASDH treatment (measured with a questionnaire) to actual surgery rates and found these to correspond well. Thus, the stated preferences directly mapped to patient treatment, i.e. we are comparing consistent preferences. We also have some other indirect measures from which we can deduce consistency. For example, the majority of neurosurgeons (at least in our study) confirmed the statement that structural practice variation for our research question exists (Chapter 4 and 5).

Generalizability and treatment effect heterogeneity

Generalizability boils down to the question to whom the effect estimate applies. In epidemiological terms: what is the "marginal patient" in this IV analysis (Table 2)? Similar to other study designs (including randomized clinical trials), in an IV analysis with a proxy for physician's preference as IV, the effect estimate also arises from the full study population, with individuals contributing with unknown weights.[30,31] In IV this means that the treatment effect stems from those patients in whom practice variation is present. We found that practice variation is present even in patients with an extreme prognosis. So, the effect estimate may well apply to the full population.

An important nuance is that the effect estimate pertains less to the patients with an extreme prognosis - because they might either never be treated or always be treated – but the precise cutoffs as to what entails an extreme prognosis cannot be well defined. I repeated the main analysis in a group of patients excluding the extreme patients at either end of the treatment spectrum (patients with one or more unreactive pupil, or who are GCS 15), and found a similar effect estimate. We, therefore, conclude that the treatment effect does apply to the total study population. And importantly, the treatment effect is robust for a middle group, which, although ill-defined, probably contributes the most to the effect estimate.

Another related aspect is that the treatment effect may differ across patients. Whether we can apply the estimate to the full study population, also depends on whether we can expect homogeneity of treatment effects, in which case, like in an RCT, the estimate effect is valid among the full study population, i.e. the estimand is the average treatment effect (ATE). We do have circumstantial evidence of heterogeneity of acute surgery. Comatose patients with a large ASDH greatly benefit because their risk of dying is greatly reduced (Chapter 3). Our retrospective study (Chapter 9) gives a suggestion of benefit in patients older than 65 years. And subgroup analyses of the main study (Chapter 10) suggest some treatment effect heterogeneity: older patients

and patients with large hematoma might benefit (Chapter 10). Nevertheless, without a convincing suggestion of treatment effect heterogeneity, the overall treatment effect is interpreted as being applicable to all patients in the study, as in other study designs.

On the other hand, when we do assume treatment effect heterogeneity, the generalizability becomes more abstract. We have to rely more on whether the application of the surgical preference is consistent across all (types of) patients; i.e. on monotonicity. In that case the estimand becomes the local average treatment effect (LATE); the treatment effect is applicable to those patients of which the treatment has been determined by the IV.[33] Monotonicity complicates matters because it is unclear whether a patient is treated under the preference that is similar to that of the instrumental variable. This inability to define who is a complier or a defier makes inferring to whom the effect estimate applies indeterminate. Thus, the inherent difficulty to define the patient population in IV effect estimation precludes recognizing the exact average treatment effect.

Importantly, patient characteristics always play a role when deciding on surgical treatment and knowledge of clinical practice suggests that for some patients even a (valid) IV plays no role in determining treatment assignment; they always or never will be treated. And just as clinicians use caution in generalizing findings from randomized trials, clinicians interpreting our study should use caution in determining whether the IV estimate applies to their patient. Treatments can have different effects in different patients. Positive and negative effects might even cancel each other.[34] IV analysis is even more complicated to interpret. A valid request might be a more extensive evaluation of the treatment heterogeneity than provided until now. These studies have not been performed yet and will be challenging since they require very large sample sizes.

We conclude that the effect estimate applies to those patients for which the neurosurgeon may hypothetically be in clinical equipoise, or in other words for which there seems to be more than one valid treatment option.

Limitations

Terminology

The presented studies are observational and inherently prone for bias. Reviewers have often argued that it would be more appropriate to use an associative denotation to describe our results ('association' instead 'does not lead to' for example). On most occasions we accepted and resigned ourselves.

We faced a considerable challenge in formulating the conclusions, finding the appropriate balance between describing the findings and causally inferring our association estimates. However, though the observational nature of our studies

certainly imposes difficult methodological challenges to infer causality, that does has not influence the initial aim of our research: to study causal effects. The use of the word 'association' in intervention research has no benefits and only confuses.[35] Or as causal inference researcher Miguel Hernan put it: "If your thinking clearly separates association from causation, make sure your writing does too."[36]

Power

For the power calculation of the IV analysis we assumed an odds ratio of 0.6, which is a fairly large treatment effect. We based this treatment effect on the available evidence and on a pilot study (Chapter 8).[28-32] We actually employed a smaller effect size than our pilot study showed (Chapter 9) to account for the uncertainty due to its small sample and the possibility residual confounding. The assumptions for the power calculation may, nevertheless, raise the question whether the absence of an effect of acute surgery or DC may be explained by an insufficient sample size to exclude small but clinically meaningful effects.

I consider that unlikely for acute surgery versus conservative treatment. All the analyses show robust odds ratios close to 1. We reported the uncertainty in these estimates through confidence intervals; not by claiming non-significance in the p-values. For DC versus craniotomy it might be the case that a smaller effect might have gone unnoticed since the confidence interval is wide (i.e. 0.5-1.5 for the original primary analysis excluding centers < 15 patients). Nevertheless, I analyzed the data since it might benefit future meta-analysis. Whereas sample size calculations are worthwhile in deciding whether a prospective study (e.g. RCT) can realistically be achieved in terms of ethics and logistics, not analyzing already collected data is not a rational strategy.[37]

Obviously, larger sample sizes are preferable to reduce statistical uncertainty. However, the current results are highly relevant for clinical practice. Practically speaking, CENTER-TBI is one of the largest studies in TBI performed so far and it is unlikely that in the near future larger studies will address these research questions.

Examining treatment preference

Center as a surrogate marker for treatment preference is an assumption of our IV analysis. Comparing the international survey to the case-mix adjusted surgery rates did allow falsifying the consistency of the treatment preferences. However, the treatment preference could have been explored more in detail. A solution could have been to present the hypothetical cases of the Dutch/Belgian survey also to neurosurgeons in Europe. Another alternative for defining the instrument would have been to determine how centers and neurosurgeons within each center treated patients with ASDH the year before patient inclusion. Such external instruments are

different from the center's case-mix adjusted surgery rate, which is an instrument defined internally, i.e. through the same data in which we estimate the effect.
Nevertheless, we estimated that both validation strategies of treatment preference, hypothetical cases to every neurosurgeon of all 65 participating centers and collection of prior treatment decisions, would not work for pragmatic reasons. Specifically, the number of questions already required a lot from the respondents. Increasing the survey would have risked noncompliance leading to missing data. The quantification of prior treatment strategies was also considered to be too time intensive.

Exploration of monotonicity

An IV study fulfilling all assumptions with homogeneous treatment effects results in an ATE estimand. However, when there is treatment effect heterogeneity, the estimand due to the monotonicity assumption becomes the LATE. External instruments as the primary IV have an advantage over defining the instrument internally; it is easier to determine the deviation from monotonicity by allowing to quantify the proportion of compliers and defiers and the impact on the effect estimate.[33,38]
Of note, the degree to which results apply to a specific patient depends not only on the proportion of the study population that consisted of these specific patients, but also on the strength of the instrument in this group. The stronger the instrument, the higher the relative contribution to the estimate. When interpreting heterogenous treatment effects in the setting of IV analysis we assume so-called stochastic monotonicity with the estimand being the strength-of-IV weighted treatment effect.[38]

Data quality and information bias

The granularity of the datasets allowed for our specific study design and analysis but also resulted in an overwhelming amount of data. Harmonization and data curation took a considerable amount of time and resources.[39] In this process arguably arbitrary decisions were made on many specific variables and data points. To check the robustness of the results for these decisions many sensitivity analyses had to be performed. Finally, the radiological data were also analyzed centrally by a dedicated radiological team, based on the National Institute of Neurological Disorders and Stroke TBI Common Data Elements,[40] which led to an enriched dataset but also to discrepancies between local and central data. Fortunately, there was good agreement for both diagnoses 'ASDH' and 'contusion/ICH' between the local (treating physicians) and central readings respectively, making misclassification bias unlikely.[41] In general, all aforementioned points in this paragraph should have been accommodated (more) in the protocol, although some could not have been anticipated.

Implications

The responses of the neurosurgical community to the comparative effectiveness study of surgery versus conservative treatment have varied (Chapter 11).[40,41] Some contest the absence of effect; after all, ever since the beginning of the previous century acute surgical evacuation for ASDH was considered common sense. Others said that it merely confirms what we already know from daily practice. The following points can be learned from our studies.

First, it will directly impact clinical practice. Our findings in part support the continued use of interventions already routinely applied in daily practice; surgical evacuation of acute subdural hematoma remains the cornerstone of treatment in life-threatening neurological deterioration. The clear effect from the meta-analysis with dramatic effect might also imply that we should operate comatose patients with a poor prognosis more often. However, this decision requires objectifying salvageability, and thus prognostication which is not easy.[42-44] On the other hand, the comparative effectiveness study in Chapter 10 shows that in certain surgical cases conservative treatment could have been employed. The 'aggressive' centers could safely treat their patients more often conservatively

Second, the inferences of the effects rely on strong evidence, derived from the largest cohorts of ASDH. This thesis is an important addition to the current low-quality literature in ASDH. The absence of a positive or negative association with outcome overall is important knowledge for all clinicians treating patients with ASDH. The findings regarding type of surgery (DC versus craniotomy) for ASDH are compatible with the current best evidence.[45] It is the largest study to date, and provides robust guidance for neurosurgeons.

Third, the wide treatment variation, from all across Europe, and an absence of benefit of either treatment preference is important knowledge for neurosurgeons treating patients with ASDH. Neurosurgeons are often 'traditional' physicians who, mostly due to the lack of appropriate evidence, understandably use clinical experience and mechanistic reasoning.[46] This mindset of 'eminence-based medicine' trained over the years and consequently passed on to the next generation, leads to a culture of having no doubts about the 'best' treatment for a specific patient, despite the lack of evidence. This intuitive decision-making under uncertainty and in an emergency setting, leads to biases that might not be recognized by the decision maker.[47,48] We hope to contribute to the neurosurgeon to become aware of these cognitive fallacies.

Fourth, this thesis presents an illustration of medical specialists taking the initiative to judiciously reflect on their practice. We live in a time of 'do-not-do lists'.[49] The lack of evidence might be interpreted unjustly as a lack of effectiveness, not in the least by stakeholders such as health care insurance companies and policy makers. With

studies like those presented in this thesis we take matters in our own hands and contribute to evidence-based decision-making on policy level.
Thus, this thesis reflects a systematic approach to evaluate common neurosurgical interventions, using high quality data and analytical approaches, and delivered results that can directly impact clinical practice.

Recommendations for clinical practice

Our studies assess effectiveness of common interventions in everyday practice in relatively unselected populations and under flexible conditions, in order to inform decisions about practice in a "real-world" setting. The inherent consequence of the IV analysis is that it is not immediately clear to what patient population the results pertain. I acknowledge this difficult interpretation and, therefore, propose specific recommendations for clinical practice. I will describe how neurosurgical practice could be affected with several cases of ASDH and propose an update of the Brain Trauma Foundation (BTF) guideline.

Applicable patient populations

The practice variation mostly affects the patients who are at neither of the extremes in terms of clinical presentation. Because an identical patient may be operated upon in one center but not in another, it naturally follows that there is more than one valid treatment option. The varying center policies thus lead to a group of patients for whom we infer clinical equipoise. The middle group is our study population (Figure 2). Because center policies are not measured per patient, it is not immediately clear what patient population the equipoise actually pertains to. However, practically, the physician in charge of the decision should make an estimation whether he/she thinks the other treatment could be a valid alternative. If not, it could be argued that the effect estimate does not apply.
There is something inherently contradictory in this line of reasoning; the lack of critical appraisal required to employ our study' conclusion is exactly what led to led to the practice variation in the first place. I expect, however, that the confrontation with this strong and consistent practice variation offers physicians the confidence to apply this kind of scrutinous, abstract thinking. I adhere hereby to the definition of clinical equipoise as the 'genuine uncertainty within the expert medical community-not necessarily on the part of the individual investigator – about the preferred treatment'.[50]

Evidence-based guideline

The BTF guideline is the most widely applied guideline in TBI.[51,52] The last version, published in 2016 was focused on severe TBI. In contrary to the previous version

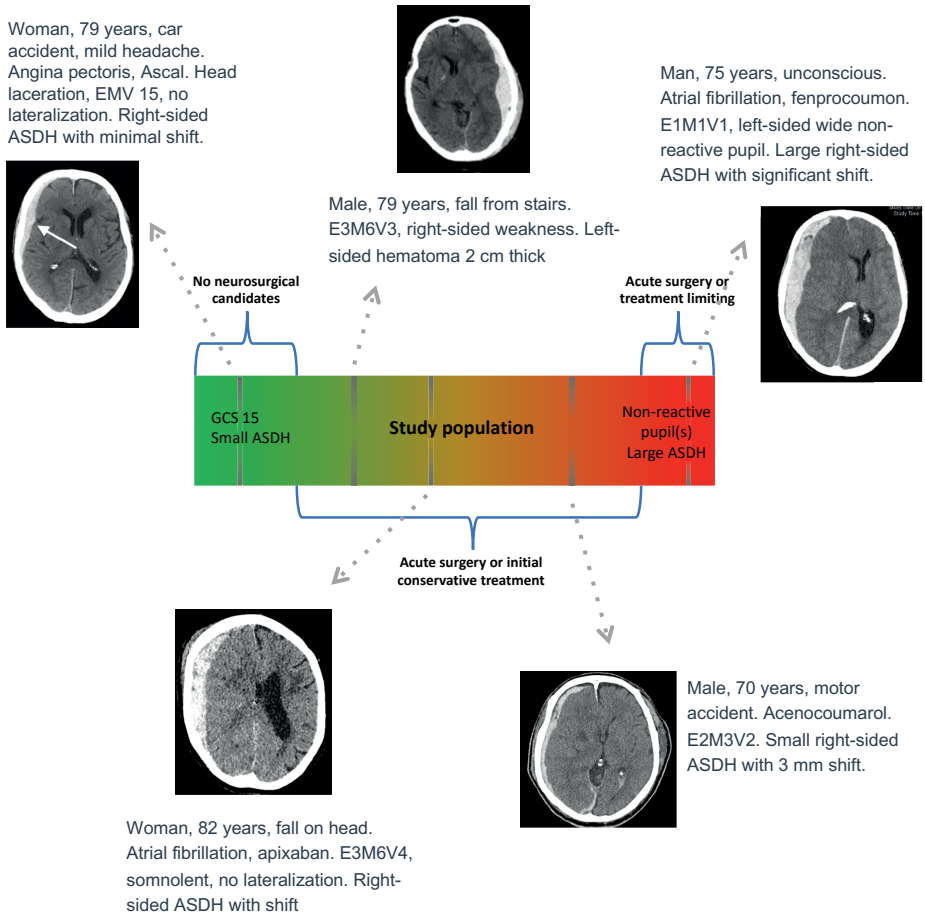


Figure 2. Acute subdural hematoma cases depicted on a scale representing the clinical spectrum with varying preference for acute surgery or (initial) conservative treatment

The right - red - end, represents patients with poor clinical characteristics for whom clinicians may perform acute (rescue) surgery to avoid death or choose for comfort measures in a treatment-limiting setting. At the left – green – end, all patients will not be operated upon due to an anticipated good prognosis without need for acute evacuation. The window between these extremes represents our study population. The exact cut-offs cannot be objectively characterized because the window is applicable to those patients for whom the neurosurgeon may hypothetically be in clinical equipoise.

of 2006, this latest version did not cover the surgical management for intracranial hematomas, probably due to the fact that no higher quality evidence has been generated since 2006.[53] We propose an extension of the latest guideline (i.e. of 2006) based on the studies of this thesis.

The underlying evidence base needs to be responsibly translated into clinically applicable, accurately graded recommendations in order to help clinicians properly

treat patients with TBI. We adhere to the methodology of the BTF on how to formulate treatment recommendations (Panel).[54] The BTF has formulated an hierarchy in evidence quality, summarized in three classes. These classes translate to recommendations while considering the methodological principles consistency, directness and precision (Panel; legend Table). The BTF guideline for the indication for surgery in ASDH can both be extended with Level IIA recommendations based on level 2 evidence. Some of the 2006 recommendations have been retained and now labeled Level III recommendations.

The BTF guideline working group in 2006 already recognized the special conditions that apply to the efficacy of acute surgical evacuation in extra-axial lesions. Specifically, a neurological deteriorating patient with a large epidural hematoma should always be surgically treated immediately based on common clinical sense while there is very little evidence to support this recommendation. In an effort to integrate obvious effects with evidence based medicine, Glasziou et al. coined the term 'dramatic effect' and explored methods to infer causality of several interventions.[55] Inspired by this approach, I evaluated the effect of surgery in ASDH for comatose patients in a meta-analysis using a historical control group (Chapter 3). The Oxford Centre for Evidence Based Medicine has proposed to upgrade observational studies with a dramatic effect to a higher evidence level.[56]

Our comparative studies (Chapter 3, 9, 10 and 12) are higher quality studies whose findings supersede those of the lesser quality investigations on which the previous recommendations for ASDH were based.

With regard to Chapter 9 and 10: though both studied acute surgery for the treatment of ASDH, a key difference is the median age difference of 68 in our Dutch study and 54 years in our European study. Indeed, both studies enrolled TBI patients consecutively but apparently in The Netherlands the average age is considerably higher. We adhere to these difference patient domains in constructing the recommendations.

Thus, the BTF guideline for the indication for surgery can be extended with level 2 recommendations. The Level IIA recommendation is based on our meta-analysis (Chapter 3) and the observational comparative effectiveness study (Chapter 10). We feel that the comparative observational study on the effectiveness of primary DC (Chapter 12) does not allow for Level IIA conclusions given the limited sample size. Therefore, we distill a Level II B recommendation.

Furthermore, our research does not support evidence-based recommendations for other surgical techniques or perioperative interventions. As the studies were observational, we recommend neurosurgeons to perform the surgical procedure according to their regular practice.

The Level III recommendations were retained from the previous guideline in 2006 and supplemented with the observational comparative effectiveness study in Chapter

9.[57] These recommendations are based on consistent effects shown in subgroups and class 3 cohort studies.

Panel: Guidelines for the Surgical management of Traumatic Brain Injury: Proposal for an Update of the Acute Subdural Hematoma Recommendations

A guideline is typically reached through consensus among a group of clinicians that are experts on the subject matter. The following paragraph should be read as a first draft for such a process. I like to emphasize therefore that this is a proposal.

RECOMMENDATIONS

Level I

• There was insufficient evidence to support a Level I recommendation for this topic.

Level II A

• Acute surgical evacuation is recommended to greatly reduce mortality among salvageable comatose patients (severe TBI).

• Acute surgical evacuation is not recommended to improve outcomes as measured by the Glasgow Outcome Scale–Extended (GOS-E) score at 6 months post-injury when considering patients with all TBI severities for which the neurosurgeon sees no clear superiority of either treatment

Level II B

• Primary DC over craniotomy in acute surgery is not recommended to improve GOS-E at 6-months.

Level III

• Acute surgical evacuation is recommended for large ASDHs, regardless of the patient's Glasgow Coma Scale score

• Acute surgical evacuation is recommended for salvageable patients older than 65

EVALUATION OF THE EVIDENCE

Quality of the Body of Evidence

With regard to whether to operate or not, three studies (Chapter 3, 9 and 10) are qualified as Class 2 evidence. The meta-analysis (Chapter 3) used a dramatic effect design. The effect was dramatic enough that confounding and immortal time bias could be sufficiently ruled out. Therefore, it was considered a Class 2 study with moderate quality of the evidence. The observational study in Chapter 9 addressing acute surgery versus conservative treatment was a retrospective comparative study comparing two centers, one with a preference for surgery and the other with a preference for conservative treatment. Residual confounding could not be sufficiently ruled out. It is considered a low-quality study with low precision and replication (in the older patient population) is advised.

For the study of Chapter 10, the quality of the evidence was moderate, because it was a multicenter, non-randomized prospective study with a very large sample size (n=1407) with multiple analyses to address confounding.

The observational study that compared primary DC to craniotomy (Chapter 12) was rated Class 2 but this study was low quality; it was a single study, with low precision, and replication is needed for higher confidence (Table).

Table. Quality of the body of evidence (acute surgery for ASDH)

Components of Overall Quality – Class 2								
Topic	**Number of Studies**	**Meta-Analysis**	**Number of Subjects**	**Class of Studies***	**Consistency (High, Moderate, Low) ****	**Directness (Direct or indirect) *****	**Precision (High, Moderate, Low) *******	**Quality of Evidence (High, Moderate, Low, or Insufficient)**
Acute surgery vs. initial conservative treatment	3 observational	1	- 12,287 (meta-analysis) - 195 - 1,407	2	Moderate	Direct	High	Moderate
Primary DC vs. craniotomy	1 observational	NA	336	2	NA	Direct	Low	Low

** Class 1 Evidence is derived from randomized controlled trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies that render them Class 2 or 3.*
Class 2 Evidence is derived from cohort studies including prospective, retrospective, and case- control. Comparison of two or more groups must be clearly distinguished. Class 2 evidence may also be derived from flawed RCTs.
Class 3 Evidence is derived from case series, databases or registries, case reports, and expert opinion. Class 3 evidence may also be derived from flawed RCTs, cohort, or case-control studies.
*** Consistency: Consistency is the extent to which the results and conclusions are similar across studies. It is rated High (all are similar), Moderate (most are similar), Low (no one conclusion is more frequent). It is NA (not applicable) when the body of evidence consists of a single study.*
**** Directness: Directness can have different definitions. We define it as whether the study population is the same as the population of interest and whether the study includes clinical rather than intermediate outcomes. Indirect is noted if the population differs; for example if the study includes both moderate and severe TBI or patients with stroke or TBI and does not separate the results by these population characteristics, or if the outcomes are not mortality or neurological function. As outlined in Methods, indirect evidence was only included if no direct evidence was found.*
***** Precision: Precision is the degree of certainty surrounding the effect estimate for a given outcome. Precision is rated as High, Moderate, and Low. How this is determined depends on the type of analysis used in a specific study but may include consideration of the range of confidence intervals or the significance level of p-values.*

Applicability
The large comparative observational study comparing acute surgery to conservative treatment took place in 65 European centers over a 3-year period, and included 1407 patients across all TBI severities. The study comparing primary DC to initial conservative management was conducted in 65 countries over a 3-year period, and included 336 patients. Both studies are considered applicable to current practice.
The second, smaller, study comparing acute surgery to conservative treatment was performed in three centers in The Netherlands. Although including all consecutive patients, the average age was 68 years which is older than expected in current practice. The conclusion of benefit of surgery in this elderly population, is in line with the subgroup analysis of the other, larger, observational study. Furthermore, in the previous version of the guideline, surgery was recommended in ASDH with thickness > 1 cm or midline shift > 0.5 cm regardless of GCS, based on Class 3 evidence. This is also in line with the suggestion of benefit in these subgroups in the larger observational study. Treatment effect heterogeneity could not formally be determined through subgroup analyses, but large hematomas showed to be associated with a strong, albeit nonsignificant, effect estimate (OR 2.7 95% CI 0.9 - 8.3). Therefore, this recommendation is retained as a Level III recommendation.

Future research

Bryan Jennett (1926-2008) knew that it was a privilege when he was asked by his chief if he would like to pursue a research project next to his residency neurosurgery. Talented residents were offered scientific research, at the time mostly fundamental research in the neurophysiology laboratory. His chief asked whether he would want to investigate how the physiological change of the reflexes in patients with a slow acting thyroid comes about. Although appreciating the honor, he answered decisively that he could not care less about the reflexes in thyroid disease. The chief reacted surprised: "Don't you want to invest in research?". "Yes" answered Jennett "but merely into clinical dilemma's I run into daily." His chief had no clue what Jennett was suggesting. Research on clinical problems? Is that scientific research at all? Jennett explained that he noticed major variability among his supervisors on which patient after a head injury to admit to the hospital. That kind of questions he would like to research.[58]

We have come a long way since then. All neurosurgical departments heavily invest in clinical research. However, still, neurosurgery has a weak evidence base.[52,59,60] Clinical decisions in neurosurgery have a history of strongly relying on personal or departmental dogma, often deduced from fundamental and basic science, and continue to do so.[61] The first RCTs addressing common surgical procedures in TBI have been conducted only the last decennium.[52,62,63] Since the famous 1996 editorial in the *British Medical Journal* on evidence-based medicine by Sackett et al.,[64] another editorial in 2008 addressed this issue for neurosurgery: "Twenty-two years later, the impact of evidence-based medicine in British neurosurgical practice has been variable and the management of some common neurosurgical conditions has not been subjected to the same scrutiny as some less common conditions. The National Health Service has tended to look more critically at expensive procedures and technology, while ignoring conditions that are dealt with in everyday practice." [65] Naturally this does not only pertain to the United Kingdom.

High-quality research begins with recognizing relevant clinical questions. Research within neurosurgery should be done by neurosurgeons because they have the unique position to appreciate the management decisions and recognize clinical relevance. There is otherwise nobody else who will investigate the clinical practice important for patients with neurosurgical diseases. Obvious constraints that explain the lagging behind is the limit in dedicated time of neurosurgeons due to the drain of clinical work and the operating theatre. Furthermore, neurosurgeons by training - and possible also by character - are highly trained decision makers that are not uncertain about their treatment preference. They might be less amenable for critical appraisal on their own actions, which is of course pivotal to clinical research. For example, the basic premise for RCTs, clinical equipoise is still often misinterpreted as doubt

or uncertainty, which are terms neurosurgeons tend to avoid in their decisions for TBI patients.[50,66] Acknowledging clinical equipoise, especially in acute settings, might be unconsciously be mistaken for uncertain or even insecure decision making. However, clinical equipoise is not at odds with treatment preferences of the individual investigators but rather reflects the collective will of a body of expert clinicians.[50] Naturally, this perceived absence of equipoise might be an important barrier for conducting RCTs. In fact, the STITCH-trauma trial that formalized the required equipoise in a inclusion criterium might attest to this problem because it was prematurely halted due to insufficient patient recruitment.[67]

There are other challenges in surgical TBI research. Case series and single treatment group cohorts are generally not suited to infer causality and there are plenty enough for common neurosurgical interventions.[61] Comparative studies especially RCTs, however, are difficult to conduct. The challenges mainly are the heterogeneity of the populations, the traditionally eminence-based neurosurgical culture, inadequate research budgets, and difficulties related to obtaining patient informed consent in an emergency situation.[12,68,69]

I propose several characteristics of future research. RCTs are preferred and should be as pragmatic as possible, directed by proper guidelines.[70] Most neurosurgical inventions have clear efficacy (they can work) but are yet to be clearly examined in terms of effectiveness (do they actually work in clinical reality?). When RCTs are difficult to conduct, observational studies with an IV analysis, when possible, should be considered to circumvent the substantial confounding by indication of acute neurosurgical interventions. Part of the solution for better neurosurgical research may be the increase of methodological knowledge among neurosurgeons. While RCTs are relatively straightforward methodologically with the major challenge being logistics and infrastructure, causal inference in observational (big) data is much harder.[71,72] Observational studies should not be considered inferior to RCTs per se.[73,74] Neurosurgeons might benefit from a strong, durable cooperation with epidemiologists and statisticians that are dedicated to the specificities of neurosurgical research.

Moreover, TBI researchers should be aware of the available informed consent alternatives to optimize patient recruitment.[68] Furthermore, I support the early assessment of new neurosurgical interventions, so that their effectiveness can be established before wide adoption. Preferably, the IDEAL framework should guide evaluation of new interventions.[75] Finally, embedding TBI research into standard clinical practice could reduce expenses and lower the threshold for study participation. Concerted efforts should be undertaken by stakeholders to develop research agendas that prioritize clinical research and allocates the scarce grants accordingly. The limited public attention through policy and targeted grants sharply contrasts the major impact TBI has on society.[76,77]

Specific research questions

When it comes to acute neurosurgical evacuation in traumatic intracranial lesions, there are several research questions I consider sufficiently pressing to make a claim on further resources. First, it is clear these large-scale studies show that the studied interventions are not uniformly beneficial. An explanation could be the inherent heterogeneity of TBI with different responses to surgery and, therefore, a neutral effect due to the mixing of systematic positive and negative effects.[34] The subgroup analyses presented in this thesis were mostly exploratory. Therefore, targeted subgroup analysis should be performed to more closely determine who benefits from surgical treatment strategies. To reduce chance findings there should be a predefined consensus on logical subgroups. I advise individual participant data meta-analysis of CENTER-TBI/Net-QuRe data and other large multicenter cohorts such as the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) project.[78] Advanced risk-stratification tools, that stratifies treatment outcome on baseline risk instead of the "one-variable-at-a-time" subgroup analysis, should be used to estimate the heterogeneous treatment effects, which allows personalize management.[79] Naturally, pragmatic trials in specific, more homogenous subgroups serves the same goal of personalize neurosurgical care.

Second, primary DC warrants further investigation in a larger study. Our own analysis (Chapter 11) was imprecise. More definite evidence will come from the RESCUE-ASDH trial, a multi-center randomized trial comparing craniotomy against DC for patients undergoing evacuation of a traumatic ASDH. Last, the effects are being considered on a limited time-frame and outcome set. I would like to have performed a costing analysis alongside our comparative studies. An hypothesis is that - costly - aggressive acute or early surgical treatment strategy might induce earlier recovery and less burden on ICU care and post-acute care rehabilitation. Although we did collect indirect measures (such as the hospital length of stay) and we described costs in our own centers,[10] we did not collect data to conduct a formal economical evaluation. Thus, the effectiveness studies on ASDH should be followed by cost-effectiveness, safety and long-term outcome analyses.

Thus, pragmatic trials targeting specific subgroups should be an important focus for future surgical TBI research. We have, therefore, grasped the nettle and have proposed an RCT, namely the Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma (RESET-ASDH trial), a study protocol for a pragmatic RCT. The Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma (RESET-ASDH) trial is an international multicenter RCT on the (cost-)effectiveness of acute neurosurgical hematoma evacuation versus initial conservative treatment in elderly with an ASDH. The study is in line with

current epidemiological developments of the rising incidence of elderly with TBI.[80,81] The studies presented in this thesis have paved the way for this trial.

Conclusion

The uncertainty about the benefits of surgery inspired the research presented in this thesis, in which I aimed to assess the effectiveness of treatment strategies for ASDH. First, I showed that good quality evidence of acute surgery versus conservative treatment to underpin guidelines is lacking, although among comatose patients, acute surgery has a clear benefit, because it leads to a large mortality reduction. Second, I demonstrated strong and consistent practice variation with regard to the fundamental question to operate or not in ASDH. Third, I argue that the value of observational studies on neurosurgical intervention for acute hematomas for practice is limited as causal inference is precluded by strong confounding by indication. One of the few analytical approaches that might allow causal interpretation is IV analysis, which requires assumptions that are not easily met. Fourth, I showed that patients treated in centers that prefer acute surgery (over conservative treatment) have an equal outcome to patients treated in centers that prefer (initial) conservative treatment. Therefore, I conclude that acute surgical evacuation of an ASDH in patients for whom equipoise exists on surgical indication may not lead to a better functional outcome compared to a strategy favoring (initial) conservative treatment. Finally, with regard to surgical technique, primary DC might not lead to better outcomes as compared to craniotomy in acute surgery in ASDH.

In light of the absence of uniform benefit, the restrictions certain neurosurgeons place on surgery for ASDH and primary DC appear justified. In light of my findings, I propose guideline recommendations for patients with ASDH. Finally, targeted subgroup analysis, risk-based prediction of heterogeneous effects and pragmatic trials should further disentangle heterogeneous treatment effects. Such future studies should be performed by neurosurgeons in collaboration with clinical epidemiologists and should have well-defined and realistic objectives to directly inform clinical practice.

REFERENCES

1. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327(7429):1459–61.
2. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. *Neurosurgery* 2005; 1183–92.
3. Fountain DM, Kolias AG, Lecky FE, et al. Survival Trends After Surgery for Acute Subdural Hematoma in Adults Over a 20-year Period. *Annals of Surgery* 2017;265(3):590–6.
4. Stein SC, Georgoff P, Meghan S, et al. 150 Years of Treating Severe Traumatic Brain Injury: A Systematic Review of Progress in Mortality. *Journal of Neurotrauma* 2010;27(7):1343–53.
5. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLoS ONE* 2016;11(8):e0161367.
6. Huijben JA, van der Jagt M, Cnossen MC, et al. Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Journal of Neurotrauma* 2017; neu.2017.5194.
7. Rayan N, Barnes S, Fleming N, et al. Barriers to compliance with evidence-based care in trauma. *J Trauma Acute Care Surg* 2012; 72(3):585–92–discussion592–3.
8. Kolias AG, Belli A, Li LM, et al. Primary decompressive craniectomy for acute subdural haematomas: results of an international survey. *Acta Neurochir* 2012;154(9):1563–5.
9. Bonds B, Dhanda A, Wade C, et al. Prognostication of Mortality and Long-Term Functional Outcomes Following Traumatic Brain Injury: Can We Do Better? *Journal of Neurotrauma* 2021;38(8):1168–76.
10. Van Dijck J, van Essen TA, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta Neurochir* 2019;161(5):875–84.
11. Sackett DL, Haynes RB, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. *Lippincott Williams and Wilkins*; 1985.
12. George P. The struggle for better research in surgery. *The Lancet* 2016;387(10032):1970.
13. Rassen JA, Brookhart MA, Glynn RJ, et al. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *Journal of Clinical Epidemiology* 2009; 62(12):1226–32.
14. Hernán M, Robins J. Causal Inference: What If. *Boca Raton: Chapman & Hall/CRC;* 2020.
15. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidem Drug Safe* 2010;19(6):537–54.
16. Laborde-Castérot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. *Journal of Clinical Epidemiology* 2015; 68(10):1232–40.
17. Wagenmakers E-J, Sarafoglou A, Aczel B. One statistical analysis must not rule them all. *Nature* 2022; 605(7910):423–5.
18. Kuramatsu JB, Biffi A, Gerner ST, et al. Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage. *JAMA* 2019; 322(14):1392–12.
19. Kuramatsu JB, Sheth KN, Huttner HB. Unmeasured Confounding in Observational Studies of Management of Cerebellar Intracranial Hemorrhage-Reply. *JAMA* 2020; 323(7):666.
20. Boef AGC, Dekkers OM, Vandenbroucke JP, le Cessie S. Sample size importantly limits the usefulness of instrumental variable methods, depending on instrument strength and level of confounding. *Journal of Clinical Epidemiology* 2014; 67(11):1258–64.
21. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; 76(1):67–80.
22. Nederlands Trial Register [Internet]. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.

23. Gantner D, Wiegers E, Bragge P, et al. Decompressive Craniectomy Practice following Traumatic Brain Injury in Comparison with Randomized Trials: Harmonized, Multi-Center Cohort Studies in Europe, the United Kingdom, and Australia. *Journal of Neurotrauma* 2022 Jun; 39(11-12):860-869.
24. Gao G, Wu X, Feng J, et al. Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study. *The Lancet Neurology* 2020;19(8):670–7.
25. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurgical FOCUS* 2009; 1–16.
26. Davies NM, Smith GD, Windmeijer F, Martin RM. Issues in the reporting and conduct of instrumental variable studies: a systematic review. *Epidemiology* 2013;24(3):363–9.
27. Boef AGC, Dekkers OM, Le Cessie S, Vandenbroucke JP. Reporting instrumental variable analyses. *Epidemiology* 2013;24(6):937–8.
28. Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clinical Epidemiology* 2018; 10:841–52.
29. Van Essen TA, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe. *BMJ Open* 2019;9(10):e033513–8.
30. Harris KM, Remler DK. Who is the marginal patient? Understanding instrumental variables estimates of treatment effects. *Health Serv Res* 1998; 33(5 Pt 1):1337–60.
31. Swanson SA, Hernán MA. The challenging interpretation of instrumental variable estimates under monotonicity. *International Journal of Epidemiology* 2017; 47(4):1289–97.
32. Ceyisakar IE, Huijben JA, Maas AIR, et al. Can We Cluster ICU Treatment Strategies for Traumatic Brain Injury by Hospital Treatment Preferences? *Neurocrit Care* 2022; 36(3):846-856.
33. Swanson SA, Miller M, Robins JM, Hernán MA. Definition and evaluation of the monotonicity condition for preference-based instruments. *Epidemiology* 2015; 26(3):414–20.
34. Gregson BA, Mitchell P, Mendelow AD. Surgical Decision Making in Brain Hemorrhage. *Stroke* 2019; 50(5):1108–15.
35. Haber NA, Wieten SE, Rohrer JM, et al. Causal and Associational Language in Observational Health Research: A Systematic Evaluation. *American Journal of Epidemiology* 2022; 19;191(12):2084-2097.
36. Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. *Am J Public Health* 2018;108(5):616–9.
37. Hernán MA. Causal analyses of existing databases: no power calculations required. *Journal of Clinical Epidemiology* 2022; 144:203–5.
38. Boef AGC, le Cessie S, Dekkers OM, et al. Physician's Prescribing Preference as an Instrumental Variable: Exploring Assumptions Using Survey Data. *Epidemiology* 2016; 27(2):276–83.
39. Maas AIR, Ercole A, De Keyser V, et al. Opportunities and Challenges in High-Quality Contemporary Data Collection in Traumatic Brain Injury: The CENTER-TBI Experience. *Neurocritical Care* 2022; 37(Suppl 2):192-201
40. Haacke EM, Duhaime A-C, Gean AD, et al. Common data elements in radiologic imaging of traumatic brain injury. *J Magn Reson Imaging* 2010;3 2(3):516–43.
41. Vande Vyvere T, Wilms G, Claes L, et al. Central versus Local Radiological Reading of Acute Computed Tomography Characteristics in Multi-Center Traumatic Brain Injury Research. *Journal of Neurotrauma* 2019; 36(7):1080–92.
42. Honeybul S, Janzen C, Kruger K, Ho KM. Decompressive craniectomy for severe traumatic brain injury: is life worth living? *Journal of Neurosurgery* 2013; 119(6):1566–75.
43. Van Dijck JT, Reith FC, van Erp IA, et al. Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management. *Journal of Neurosurgical Sciences* 2018; 62(2):153–77.
44. Van Dijck J, van Essen TA, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta Neurochir* 2019;161(5):875–84.
45. Hartings JA, Vidgeon S, Strong AJ, et al. Surgical management of traumatic brain injury: a comparative-effectiveness study of 2 centers. *Journal of Neurosurgery* 2014;120(2):434–46.
46. Ergina PL, Cook JA, Blazeby JM, et al. Challenges in evaluating surgical innovation. *The Lancet* 2009; 374(9695):1097–104.

47. Kelly ML, Sulmasy DP, Weil RJ. Spontaneous intracerebral hemorrhage and the challenge of surgical decision making: a review. *Neurosurgical FOCUS* 2013;34(5):E1.
48. Kahneman D. Thinking, Fast and Slow. *Macmillan* 2011.
49. Wammes JJG, van den Akker-van Marle ME, Verkerk EW, et al. Identifying and prioritizing lower value services from Dutch specialist guidelines and a comparison with the UK do-not-do list. *BMC Med* 2016; 14(1):196.
50. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317(3):141–5.
51. Volovici V, Ercole A, Citerio G, et al. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. *World Neurosurg* 2019; 125:e515–20.
52. Volovici V, Steyerberg EW, Cnossen MC, et al. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. Journal of Neurotrauma 2019; 36(22):3183–9.
53. Bullock MR, Chesnut R, Ghajar J, et al. Surgical Management of Traumatic Brain Injury Guidelines. *Neurosurgery* 2006; 58(Supplement):S2–1–S2–3.
54. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; 80(1):6–15.
55. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007; 334(7589):349–51.
56. Howick J, Library ICJL, Glasziou P, et al. "The Oxford Levels of Evidence 2." Oxford Centre for Evidence-Based Medicine. Available from: http://www.cebm.net/index.aspx?o=5653
57. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; 58(3 Suppl):S16–24–discussionSi–iv.
58. Stam J, Renckens C, Bouma J, Hijdra A, Van Gijn J, Vermeulen R. De Kritieken. Amsterdam: *Off Page* 2011.
59. Mansouri A, Cooper B, Shin SM, Kondziolka D. Randomized controlled trials and neurosurgery: the ideal fit or should alternative methodologies be considered? Journal of *Neurosurgery* 2016; 124(2):558–68.
60. Martin E, Muskens IS, Senders JT, et al. Randomized controlled trials comparing surgery to non-operative management in neurosurgery: a systematic review. *Acta Neurochir (Wien)* 2019; 161(4):627-634.
61. Yarascavitch BA, Chuback JE, Almenawer SA, et al. Levels of evidence in the neurosurgical literature: more tribulations than trials. *Neurosurgery* 2012; 71(6):1131–7–discussion1137–8.
62. Vranos G, Tatsioni A, Polyzoidis K, Ioannidis JPA. Randomized trials of neurosurgical interventions: a systematic appraisal. *Neurosurgery* 2004; 55(1):18–25–discussion25–6.
63. Azad TD, Veeravagu A, Mittal V, et al. Neurosurgical Randomized Controlled Trials-Distance Travelled. *Neurosurgery* 2018; 82(5):604–12.
64. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312(7023):71–2.
65. Farah JO, Varma TRK. Evidence-based neurosurgery—is it possible? *Br J Neurosurg* 2008; 22(4):461–2.
66. Helmy A, Timofeev I, Santarius T, Hutchinson P. What constitutes Clinical Equipoise? *Br J Neurosurg* 2009; 23(5):564–5.
67. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with traumatic intracerebral haemorrhage [STITCH(Trauma)]: the first randomised trial. *Journal of Neurotrauma* 2015; 32(17):1312-1323.
68. Kompanje EJO, van Dijck JTJM, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. *The Lancet Neurology* 2020; 19(12):1033–42.
69. Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. *Critical Care* 2011; 15(3):R127.
70. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; 350.
71. Bergstrom CT, West JD. Calling Bullshit. *New York: Penguin Random House 2021.*
72. Nørgaard M, Ehrenstein V, Vandenbroucke JP. Confounding in observational studies based on large health care databases: problems and potential solutions – a primer for the clinician. *Clinical Epidemiology* 2017; Volume 9:185–93.
73. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. *Evid Based Med* 2016; 21(4):125–7.
74. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy

of research designs. *N Engl J Med* 2000; 342(25):1887–92.
75. McCulloch P, Altman DG, Flum DR, et al. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet* 2009; 374(9695):1105–12.
76. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12):987–1048.
77. Bowman K, Matney C, Berwick DM. Improving Traumatic Brain Injury Care and Research: A Report From the National Academies of Sciences, Engineering, and Medicine. *JAMA* 2022; 327(5):419–20.
78. Yue JK, Vassar MJ, Lingsma HF, et al. Transforming research and clinical knowledge in traumatic brain injury pilot: multicenter implementation of the common data elements for traumatic brain injury. *Journal of Neurotrauma* 2013; 30(22):1831–44.
79. Kent DM, Paulus JK, van Klaveren D, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. *Ann Intern Med* 2020;172(1):35–45.
80. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013 ;9(4):231-6.
81. Steyerberg EW, EW, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *The Lancet Neurology* 2019; 18(10):923–34.

APPENDICES

SAMENVATTING

In het **Hoofdstuk 1** wordt de huidige literatuur over de chirurgische behandeling van het acuut subduraal hematoom (ASDH) in traumatisch hersenletsel (THL) samengevat. Het ASDH is de meest voorkomende traumatische hersenbloeding en operatieve verwijdering van deze bloeding is een van de meest voorkomende acute neurochirurgische operaties.[1] Het ASDH kan met een spoedoperatie, een craniotomie of een decompressieve craniectomie (DC), behandeld worden of conservatief met nauwkeurige monitoring. Neurochirurgen die een voorkeur hebben voor een spoedoperatie schatten in dat er bij een groot hematoom neurologische verslechtering optreedt die niet meer teruggedraaid kan worden. Zij worden hierin ondersteund door '*The Brain Trauma Foundation*' (BTF) richtlijn, ontwikkeld in 2005 door een internationaal panel van experts, die voorschrijft dat elk ASDH met een dikte >10mm en een middellijn verschuiving van meer dan 5 mm operatief geëvacueerd moet worden, ongeacht de neurologisch conditie.[2,3]Aan de andere kant, neurochirurgen die in soortgelijke gevallen een voorkeur hebben voor conservatieve behandeling met monitoring, willen de patiënt niet blootstellen aan een risicovolle hersenoperatie zonder een meer precieze inschatting van de kans op neurologische achteruitgang als er geen spoedoperatie gebeurt. Het kan beargumenteerd worden dat de richtlijn en het beschikbare bewijs niet afdoende zijn om de behandeling te sturen, omdat kwalitatief goede studies ontbreken.

Het gebrek aan degelijk bewijs was de motivatie voor dit proefschrift. Vervolgens hebben we de onderzoeksvragen geformuleerd:

I. Wat is het huidige bewijs van de effectiviteit van chirurgische behandeling van het ASDH?
II. Wat is de huidige praktijk van chirurgie voor ASDH in Europa?
III. Welke studie opzet en analyse zijn geschikt om het effect van neurochirurgie bij ASDH te bepalen?
IV. Wat is de effectiviteit van verschillende behandelstrategieën (acute chirurgie versus conservatieve behandeling, en DC versus craniotomie) bij ASDH?

Om deze onderzoeksvragen te beantwoorden hebben we daarna de cohorten van '*Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury*' (CENTER-TBI) en '*Neurotraumatology Quality Registry*' (Net-QuRe) opgezet.

In **DEEL I** wordt het huidige bewijs verder uitgediept. De samenvatting in **Hoofdstuk 2** geeft een overzicht van vergelijkende studies bij chirurgisch THL. **Hoofdstuk 3** is een systematisch review over het effect van chirurgie bij ASDH. In het eerste gepubliceerde systematische review over de mortaliteit bij ASDH hebben we 102 studies met 12.287 patiënten opgenomen. De totale mortaliteit bij ASDH was 48% (95% betrouwbaarheidsinterval [BI] 44-53%). Bij een bepaalde subgroep ernstig

aangedane patiënten, de comateuze patiënten, bleek chirurgie gepaard te gaan met een mortaliteit 41% (95% BI 31-51%). Het mortaliteitsrisico geassocieerd met de conservatieve behandeling van comateuze ASDH-patiënten was 81% (95% BI 56-98%). Als we vervolgens aannemen dat een operatie een dramatisch effect heeft, leidt chirurgische evacuatie tot een mortaliteitsreductie van 40%.

In **DEEL II** beschrijven we de huidige praktijk van neurochirurgische behandelingen van THL. De eerste studie, **Hoofdstuk 4,** is een beschrijvend onderzoek in Nederland en België over hoe patiënten met ASDH worden behandeld.
De onderzoeksvraag is of de verschillen in behandeling van het ASDH het resultaat zijn van verschillende voorkeuren onder neurochirurgen. Ze kregen typische casus van THL en een ASDH online voorgelegd. Zestig neurochirurgen vulden de vragenlijst in (respons 65%). Voor patiënten met ernstig THL en ASDH (drie gevallen) was er een bescheiden variatie in de beslissing om het hematoom al dan niet operatief te evacueren; respectievelijk 88%, 100% en 77% zou een spoedoperatie uitvoeren. De variatie was meer uitgesproken voor patiënten met een matige-ernstig of licht THL. Bijvoorbeeld, bij een casus van een 79-jarige man met een licht THL en een vrij groot ASDH, koos 1 op de 7 (14%) neurochirurgen in één regio een chirurgische strategie in vergelijking met 9 op de 10 (90%) in een andere regio. Ondanks deze duidelijke praktijkvariatie, zou desalniettemin minder dan de helft van (dezelfde) neurochirurgen (48%) deze beslissing open staan voor randomisatie in een onderzoek. Deze praktijkvariatie en het feit dat deze groep, lichte of matig-ernstige THL en ASDH, de meerderheid van de patiënten met een ASDH vertegenwoordigt, waren de aanzet tot ons verder onderzoek. De praktijkvariatie ondersteunt de methodologie van het *Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury* (CENTER-TBI)-initiatief, en gaf vorm aan het Nederlandse *NeuroTraumatology Quality Registry* (Net-QuRe)-initiatief.[4,5]
Dit overzicht van de huidige neurochirurgische zorg in Nederland en België wordt in **Hoofdstuk 5** aangevuld met een enquête over verschillen in neurochirurgische behandelstrategieën voor THL in Europa. De enquête werd ingevuld door 68 centra (100%), voornamelijk door neurochirurgen (78%). Alle centra bieden 24/7 acute neurochirurgische dekking, in ieder geval binnen 30 minuten. Het merendeel van het aantal neurochirurgische THL-operaties is vanwege het ASDH, gemiddeld 25 gevallen per jaar (per centrum). Veertig procent van de respondenten vermeldden een absolute dikte- of volumedrempel voor evacuatie van een ASDH. De meeste respondenten (78%) maken de keuze voor het wel of niet uitvoeren van een primaire DC bij een ASDH pas tijdens de operatie afhankelijk van de mate van zwelling van de hersenen. Voor ICH zou 3% direct, dat wil zeggen bij presentatie, een chirurgische evacuatie uitvoeren om secundaire achteruitgang te voorkomen en 66% alleen in

geval van klinische achteruitgang. Behandelingsstrategieën varieerden aanzienlijk tussen regio's, met name voor de drempel voor ASDH-chirurgie en DC voor refractair verhoogde ICP. 31% van de centra meldden variatie binnen het eigen ziekenhuis voor de indicatie van een ICP-monitor en 43% voor het evacueren van massalaesies. De resultaten van de vragenlijst wijzen op mogelijke onderzoeksvragen voor vergelijkend effectiviteitsonderzoek (*comparative effectiveness research* [CER]).

In **DEEL III** wordt ingegaan op de voorbereiding van het ontwerp van ons onderzoek, de gemaakte methodologische keuzes om onze effectiviteitsdoelstellingen te bereiken. Het beschrijft in het bijzonder twee casestudies en literatuuroverzicht over het opzetten van een observationele studie om de effectiviteit van acute intracraniële interventies te bepalen.
Observationele studies vormen het alternatief voor de gouden standaard van een gerandomiseerde gecontroleerde studie (RCT). Een belangrijke uitdaging in observationeel onderzoek naar interventies is *confounding by indication*, een uitdrukking die verwijst naar een situatie waarin patiëntkenmerken, in plaats van de interventie, onafhankelijke voorspellers zijn van de uitkomst. Het doel van de studie in **Hoofdstuk 6** was om de validiteit van methoden om te corrigeren voor confounding in observationele studies van interventies bij THL te onderzoeken. Er zijn drie grote datasets gebruikt waarin de interventies intracraniële druk (ICP) monitoring, intracraniële operatie en primaire verwijzing werden onderzocht. Multivariabele regressie, propensity score matching en instrumentele variabele (IV) analyse werden vergeleken. Bovendien werden deze methoden in een simulatiestudie vergeleken in hoeverre zij ongemeten confounding kunnen corrigeren. Voor alle drie de interventies resulteerden multivariabele regressie en propensity score matching in negatieve schattingen van het behandeleffect (OR variërend van 0,80 tot 0,92), terwijl de IV-analyse aangaf dat zowel ICP-monitoring als intracraniële operatie gunstig zou zijn (OR per 10% verandering 1,17; 95% BI 1,01-1,42 en 1,42; 95% BI 0,95-1,97). In onze simulatiestudie resulteerden multivariabele regressie en propensity score matching in een ongeldige schatting van het behandeleffect in het geval van ongemeten confounders (OR variërend van 0,90 tot 1,03). De IV-benadering gaf een schatting in dezelfde richting als het gesimuleerde effect (OR per 10% verandering 1,04-1,05), maar was statistisch inefficiënt. De conclusie is dat IV-analyse een meer valide schatting van het behandelingseffect zou kunnen geven in vergelijking met conventionele analytische methoden. De bevindingen suggereerden echter ook dat alternatieve methoden gelijktijdig moeten worden gebruikt om de geloofwaardigheid van effectschatting te versterken.[6]
Hoofdstuk 7 is een ingezonden brief waarin we de validiteit van de analyse in een observationeel onderzoek naar het effect van chirurgische evacuatie van een

vergelijkbare aandoening, het spontaan intracerebellair hematoom, betwijfelen.[7] We stellen voor dat het onderzoek bij voorkeur ook een IV-effectschatting toevoegt om betrouwbaar te corrigeren voor de ongemeten confounding. Geïnspireerd door onze studie in het vorige hoofdstuk, suggereren we dat de gegevens een op centrumvoorkeur gebaseerde IV-analyse mogelijk maken, omdat het cohort afkomstig is van 64 centra met waarschijnlijk verschillende behandelvoorkeuren. In hun reactie vermelden de auteurs deze analyse uitgevoerd te hebben en concluderen vergelijkbare resultaten als met hun oorspronkelijke schattingen voor de onderzochte primaire en secundaire uitkomsten.[8]

In **Hoofdstuk 8** werken we een onderzoeksprotocol uit. We ontwerpen een deel van het CENTER-TBI cohort en zetten Net-QuRe op met als doel te beantwoorden wie acuut chirurgisch moet behandelen bij ASDH, bij een en wanneer een primaire DC verricht moet worden. De studie is een vergelijkend effectiviteitsonderzoek met een zogenoemd *comparative effectiveness research* (CER) design, een multicenter prospectief observationeel cohortonderzoek dat gebruik maakt van variatie in neurotraumazorg om vergelijkbare studiegroepen te creëren. Het ontwerp met meerdere centra is nodig om genoeg patiënten met verschillende behandelingsstrategieën voor ASDH en ICH te krijgen. Patiënten met een ASDH en/of een ICH worden geïncludeerd. Inherent aan het observationele design van deze studie, worden de behandelingen besloten door de neurochirurg, eventueel op basis van lokale chirurgie- en intensive care-protocollen. De resulterende variatie in de behandeling wordt geaccepteerd en geanalyseerd. Om inzicht te krijgen in deze variatie wordt gedetailleerde informatie verzameld over de redenen voor specifieke interventies of behandelstrategieën. De onderzochte interventies zijn ten eerste acute chirurgie, gedefinieerd als chirurgie direct na de eerste CT bij presentatie, versus conservatieve behandeling zonder chirurgie of chirurgie in tweede instantie, en ten tweede craniotomie versus DC. De primaire uitkomstmaat is de *Glasgow Outcome Score-Extended* na 6 maanden. Secundaire uitkomstmaten zijn onder meer ziekenhuissterfte, kwaliteit van leven en neuropsychologische tests. In de primaire analyse zal het effect van behandelvoorkeur (gedefinieerd als het percentage patiënten waarbij de onderzochte interventie de voorkeur heeft) per ziekenhuis worden geanalyseerd met *random effects, proportional odds, ordinal* regressiemodellen, gecorrigeerd voor patientkarakteristieken. Gevoeligheidsanalyses zullen (conventionele) multivariabele regressiemodellering en propensity score matching omvatten, waarbij de behandeling op patiëntniveau wordt gedefinieerd. In CENTER-TBI en Net-QuRe samen werden ongeveer 1000 patiënten met ASDH en 750 patiënten met ICH verwacht, afkomstig van ongeveer 70 centra. Deze steekproeven leiden tot een power van 80% om het verschil te detecteren (uitgaande van een tweezijdige significantie 0,05).

DEEL IV is gericht op de effectiviteit van chirurgie bij ASDH. Tijdige evacuatie van een zich uitbreidend traumatisch intracraniaal hematoom bij een patiënt met een verslechterend bewustzijnsniveau is levensreddend. De meeste patiënten met een traumatisch intracraniaal hematoom presenteren zich echter met een beperkt gedaald of hoog bewustzijnsniveau. Vooral bij patiënten met een ASDH of een ICH bestaat er onzekerheid over de indicaties, het tijdstip van de operatie en het type operatie, wat tot uiting komt in grote praktijkvariaties.

We beginnen met een observationeel *comparative effectiveness* onderzoek in twee traumaregio's in Nederland in **Hoofdstuk 9**. Hierin vergelijken we behandelstrategieën op centrumniveau in plaats van op patiëntniveau om de confounding te verminderen. De regio's zijn geografisch niet overlappend en vallen onder afzonderlijke neurochirurgische afdelingen. Deze regio's zijn gekozen vanwege hun – a priori gedefinieerde – uiteenlopende behandelvoorkeuren die zijn afgeleid uit het onderzoek in hoofdstuk 7. De patiëntkenmerken waren vergelijkbaar tussen regio's. De mediane leeftijd was met 68 jaar relatief hoog (interkwartielafstand [IKA], 54-76). Primaire evacuatie werd uitgevoerd bij 84% van de patiënten in regio A en bij 65% van de patiënten in regio B ($p < 0,01$). De strategie van chirurgische evacuatie was geassocieerd met een significant lagere kans op een ongunstige uitkomst (OR 0,53; 95% BI: 0,27-1,02) 3-9 maanden na het letsel. We concludeerden dus dat een agressieve chirurgische managementstrategie geassocieerd zou kunnen zijn met een betere uitkomst bij een oudere populatie met traumatische ASDH's. De belangrijke beperking is echter dat andere regionale verschillen deze bevinding kunnen verklaren. De hogere incidentie van klinische verslechtering in een van deze regio's kan bijvoorbeeld het gevolg zijn van het grotere aantal secundaire verwijzingen. Primaire presentatie aan een neurochirurgisch centrum heeft een nauwe relatie met de tijd tot operatie en zou zelfs de uitkomst van de patiënt kunnen verbeteren.[9] En hoewel de primaire verwijzing en andere verschillen gebalanceerd worden door andere (gemeten) confounders - de cohorten van beide regio's hebben immers een vergelijkbare voorspelde uitkomst volgens een gevalideerd prognostisch model – is restverstoring mogelijk. We stelden grotere vergelijkende studies met meer ziekenhuizen voor om dit effect van chirurgie en de generaliseerbaarheid betrouwbaarder en nauwkeuriger te onderzoeken (Hoofdstuk 8).

In **Hoofdstuk 10** analyseerden we gegevens van 1407 patiënten met een ASDH en ontdekten dat het aandeel patiënten dat een spoedoperatie onderging varieerde van 6 tot 52% (IKA = 13-35%) tussen centra. De daaruit volgende gecorrigeerde mediane odds ratio (MOR) van 1,8 ($p < 0,001$) kan worden geïnterpreteerd als een twee keer grotere kans dat een identieke patiënt een spoedoperatie zal ondergaan in het ene versus een ander willekeurig centrum. Voor acute chirurgie bij ASDH vonden we dat de centrumvoorkeur voor een acute chirurgische strategie boven die van een

(initiële) conservatieve behandeling niet significant geassocieerd was met een betere uitkomst (odds ratio [OR] 0,92 [95% BI 0,77 tot 1,09]). Uitgestelde chirurgie binnen de conservatieve groep (n=982) trad op bij 107 patiënten (11%) na een mediaan van 19,1 uur (IKA 8,1-84,6).
Deze resultaten moeten worden geïnterpreteerd in het licht van de *comparative effectiveness* opzet en impliceren geen algehele afwezigheid van effect van chirurgie. De resultaten zijn van toepassing op die patiënten voor wie de neurochirurg geen duidelijke superioriteit van beide behandelingen ziet. Daarom concluderen we dat acute chirurgische evacuatie van een ASDH bij patiënten waarvoor *clinical equipoise* bestaat, mogelijk niet leidt tot een beter resultaat in vergelijking met (initiële) conservatieve behandeling.
In **Hoofdstuk 11** reageren we op een ingezonden brief waarin bepaalde aspecten van onze studie in Hoofdstuk 10 worden besproken.[10]
In **Hoofdstuk 12** onderzochten we de effectiviteit van een primaire DC in vergelijking met een craniotomie bij patiënten met ASDH, door opnieuw gebruik te maken van de praktijkvariatie. Van de 336 geïncludeerde patiënten, ondergingen 91 (27%) patiënten een DC en 245 (63%) een craniotomie voor ASDH evacuatie. Het type primaire acute chirurgie voor ASDH varieerde sterk tussen centra: het aandeel patiënten dat een primaire DC in plaats van een craniotomie onderging, varieerde van 6 tot 67% (IKA = 12-26%) met een gecorrigeerde MOR voor primaire DC van 2,7 ($p < 0,001$). Een voorkeur van een centrum voor primaire DC in plaats van craniotomie om het hematoom te evacueren was niet geassocieerd met een betere uitkomst (OR per 14% (IKA) meer primaire DC in een centrum 0.9 [95% BI 0,7 tot 1,1], n = 200). Deze bevindingen zijn wederom van toepassing op die patiënten waarvoor *clinical equipoise* bestaat.

De beslissing om al dan niet te opereren bij patiënten met een traumatische ASDH kan in veel gevallen een neurochirurgisch dilemma zijn. In dit proefschrift is een verscheidenheid aan onderwerpen op het gebied van de chirurgische behandeling van THL bestudeerd en besproken. Huidige behandelstrategieën werden beschreven, klinische kenmerken van het patiëntendomein (chirurgische THL) werden bestudeerd en de optimale onderzoeksmethodologie om de effectiviteitsvragen te beantwoorden werd onderzocht. Dit proefschrift draagt bij aan de beoordeling van chirurgische ingrepen bij THL en zal toekomstig onderzoek beïnvloeden.

REFERENTIES

1. Compagnone C, Murray GD, Teasdale GM, et al. The Management of Patients with Intradural Post-Traumatic Mass Lesions: A Multicenter Survey of Current Approaches to Surgical Management in 729 Patients Coordinated by the European Brain Injury Consortium. Neurosurgery 2005;:1183–92.
2. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. Neurosurgery 2006;58(3 Suppl):S16–24–discussionSi–iv.
3. Bullock MR, Chesnut R, Ghajar J, et al. Surgical management of traumatic parenchymal lesions. Neurosurgery 2006;58(3 Suppl):S25–46–discussionSi–iv.
4. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 2015;76(1):67–80.
5. Nederlands Trial Register [Internet]. Amsterdam: Academic Medical Center (The Netherlands). 2004 Oct 26. Identifier Trial NL5761; 2016 July 28. Available from: https://www.trialregister.nl/trial/5761.
6. Laborde-Castérot H, Agrinier N, Thilly N. Performing both propensity score and instrumental variable analyses in observational studies often leads to discrepant results: a systematic review. Journal of Clinical Epidemiology 2015;68(10):1232–40.
7. Kuramatsu JB, Biffi A, Gerner ST, et al. Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage. JAMA 2019;322(14):1392–12.
8. Kuramatsu JB, Sheth KN, Huttner HB. Unmeasured Confounding in Observational Studies of Management of Cerebellar Intracranial Hemorrhage-Reply. JAMA 2020;323(7):666.
9. Stone JL, Lowe RJ, Jonasson O, et al. Acute subdural hematoma: direct admission to a trauma center yields improved results. The Journal of Trauma: Injury, Infection, and Critical Care 1986;26(5):445–50.
10. Beucler N. Treatment of acute subdural haematoma. The Lancet Neurology 2022;21(12):1080.

ACKNOWLEDGMENTS (DANKWOORD)

Allereerst bedank ik graag alle patiënten die vrijwillig hebben deelgenomen aan de Net-QuRe en CENTER-TBI studies. Verder bedank ik ook graag de volgende personen:

Mijn promotoren Wilco Peul, Hester Lingsma en co-promotor Godard de Ruiter.

Mijn collega onderzoekers
Hugo den Boogert, Iris Ceyisakar, Maryse Cnossen, Véronique De Keyser, Bart Depreitere, Jeroen van Dijck, Inge van Erp, Willemijn van Erp, Iain Haitsma, Majanka Heijenbrok-Kal, Peter Hutchinson, Bram Jacobs, Mathieu van der Jagt, Angelos Kolias, Andrew Maas, Geoff Manley, Amy Markowitz, David Menon, Jan Paul Muizelaar, Joukje van der Naalt, Daan Nieboer, Lianne Peppel, Dana Pisică, Lodwijk Res, Gerard Ribbers, Jan Schoones, Guus Schoonman, Ranjit Singh, Ewout Steyerberg, Victor Volovici, Robert Walchenbach, Eveline Wiegers, Alexander Younsi, John Yue.

Beste (reserve-)paranimfen en vrienden
Liron Duraku
Marnix Guijt
Victor Harmse

De *Trauma Intervention Prognostic Study Group*
J. Blom-De Vreugd, M. de Gooijer-Van Zwieten, E. Knijnenberg, M. Nuyten, J. Videler-Pitlo, M. de Raaf, L. Smakman, en R. van Schaik-Dassen (manager).

Mijn collega's van de Klinische Epidemiologie, Leids Universitair Medisch Centrum
Suzanne Cannegieter, Ton de Craen †, Olaf Dekkers, Tamara Wienen-Groen, Banne Németh, Frits Rosendaal, Yvonne Souverein.

Assistenten en staf van het Universitair Neurochirurgisch Centrum Holland, Leids Universitair Medisch Centrum, Haaglanden Medisch Centrum en HAGA ziekenhuis.

Mijn familie
Atie, Bernard, Lous, Ank, Henk, Tia, Iris, Merle, Renée, Niek, José, Rien en mijn ouders.

Floris, Philip en Chrisje

LIST OF PUBLICATIONS

* Publications for this thesis

PEER-REVIEWED ARTICLES

Yue JK, Yuh EL, .., **Van Essen TA**, et al. Isolated Traumatic Subarachnoid Hemorrhage on Initial Head CT May Not Be Isolated: A TRACK-TBI Study.
Submitted

Pisică D, Volovici V, .., **Van Essen TA**, et al. Clinical and Imaging Characteristics, Care Pathways and Outcomes of Traumatic Epidural Hematomas: A CENTER-TBI Study
Submitted

Yue JK, Lee YM, .., **Van Essen TA**, et al. Performance of the IMPACT and CRASH Prognostic Models for Traumatic Brain Injury in a Contemporary Multicenter Cohort: A TRACK-TBI Study
Submitted

Van Erp IAM, **Van Essen TA**, Kompanje EJO, et al. Treatment-limiting decisions for traumatic brain injury in The Netherlands
Under review

Riemann L, Mikolic A, .., **Van Essen TA**, et al. Computed Tomography Lesions and Their Association with Global Outcome in Young People with Mild Traumatic Brain Injury.
J Neurotrauma. 2023 Feb 24.

Adegeest CY, Van der Gaag NA, **Van Essen TA**, Ter Wengel PV. Neurochirurgische dilemma's bij secundaire neurologische achteruitgang na spinale schotverwondingen
Submitted

Yue JK, Krishnan N, .., **Van Essen TA**, et al. Neuroworsening in the Emergency Department is a Predictor of Traumatic Brain Injury Intervention and Outcome: A TRACK-TBI Pilot Study
J Clin Med. 2023 Mar 3;12(5):2024.

Yue JK, Kobeissy FH, .., **Van Essen TA**, et al. Neuroinflammatory Biomarkers for Traumatic Brain Injury Diagnosis and Prognosis: A TRACK-TBI Pilot Study
Neurotrauma Rep. 2023 Mar 24;4(1):171-183.

* **Van Essen TA**, Lingsma HF, Steyerberg EW, et al. Acute subdural hematoma: answering the clinically relevant question
The Lancet Neurol. 2022 Dec;21(12):1080-1081.

Maas AIR, Menon DK, .., **Van Essen TA**, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research.
The Lancet Neurol. 2022. Nov;21(11):1004-1060.

Singh RD, **Van Essen TA**, Kloet A. Het (sub)acuut subduraal hematoom en het lucide interval.
Submitted

Vreeburg RJG, Singh RD, et al, **Van Essen TA**. The optimal timing of cranioplasty following decompressive craniectomy in traumatic brain injury: A prospective multicenter observational study within CENTER-TBI and NeT-QuRe.
Submitted

Van Essen TA,† Van Erp IAM,† Lingsma HF, et al. Early Surgery versus Conservative Treatment in Patients with Traumatic Intracerebral Hematoma: a CENTER-TBI study.
Under review
† *Equal contribution*

Howe EI, Zeldovich M, .., **Van Essen TA**, et al. Rehabilitation and outcomes after complicated vs uncomplicated mild TBI: results from the CENTER-TBI study.
BMC Health Serv Res. 2022 Dec 16;22(1):1536.

*** Van Essen TA**, Van Erp IAM, Lingsma HF, et al. Comparative Effectiveness of Decompressive Craniectomy versus Craniotomy for Traumatic Acute Subdural Hematoma: a CENTER-TBI study.
Under review

Van Essen TA,† Hoogslag VDN,† Dijkman MD, et al. A multicentre retrospective cohort study on health-related quality of life after traumatic acute subdural haematoma: does cranial laterality affect long-term recovery?
BMC Neurol. 2022 Aug 1;22(1):287.
† *Equal contribution*

Åkerlund CAI, Holst A, .., **Van Essen TA**, et al. Clustering identifies endotypes of traumatic brain injury in an intensive care cohort: a CENTER-TBI study.
Crit Care. 2022 Jul 27;26(1):228.

Van der Vlegel M, Mikolić A, .., **Van Essen TA**, et al. Health care utilization and outcomes in older adults after Traumatic Brain Injury: A CENTER-TBI study.
Injury. 2022 Aug;53(8):2774-2782.

*** Van Essen TA**, Res LCS, Schoones JW, et al. The Mortality Reduction of Acute Surgery in Traumatic Acute Subdural Hematoma since the 19th Century: Systematic Review and Meta-analysis with Dramatic Effect Is surgery the obvious parachute?
J Neurotrauma. 2023 Jan;40(1-2):22-32.

Van Erp IAM, Michailidou I, **Van Essen TA**, et al. Tackling Neuroinflammation After Traumatic Brain Injury:Complement Inhibition as a Therapy for Secondary Injury.
Neurotherapeutics. 2022 Oct 12.

Bockhop F, Zeldovich M, .., **Van Essen TA**, et al. Measurement invariance of six language versions of the post-traumatic stress disorder checklist for DSM-5 in civilians after traumatic brain injury.
Sci Rep. 2022 Oct 4;12(1):16571.

Riemann L, Alhalabi OT, .., **Van Essen TA**, et al. Concomitant spine trauma in patients with traumatic brain injury: Patient characteristics and outcomes.
Front Neurol. 2022 Aug 18;13:861688.

Volovici V, Pisică D, .., **Van Essen TA**, et al. Comparative effectiveness of intracranial hypertension management guided by ventricular versus intraparenchymal pressure monitoring: a CENTER-TBI study.
Acta Neurochir (Wien). 2022 Jun 1.

Wilson L, Horton L, .., **Van Essen TA**, et al. Tailoring Multi-Dimensional Outcomes to Level of Functional Recovery after Traumatic Brain Injury.
J Neurotrauma. 2022 Oct;39(19-20):1363-1381.

Thomas I, Dickens AM, .., **Van Essen TA**, et al. Serum metabolome associated with severity of acute traumatic brain injury.
Nat Commun. 2022 May 10;13(1):2545.

*** Van Essen TA**, Lingsma HF, Pisică D, et al. Surgery versus conservative treatment for traumatic acute subdural haematoma: a prospective, multicentre, observational, comparative effectiveness study.
The Lancet Neurol. 2022 May 5:S1474-4422(22)00166-1.

Singh RD, Van Dijck JTJM, et al, **Van Essen TA**. Challenges Encountered in Surgical Traumatic Brain Injury Research: A Need for Methodological Improvement of Future Studies.
World Neurosurg. 2022 May;161:410-417.

Singh RD, **Van Essen TA**,† Van Dijck JTJM,† et al. Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma (RESET-ASDH trial): study protocol for a pragmatic randomized controlled trial with multicenter parallel group design.
Trials. 2022 Mar 29;23(1):242.
† *Equal contribution*

Ceyisakar IE, Huijben JA, .., **Van Essen TA**, et al. Can We Cluster ICU Treatment Strategies for Traumatic Brain Injury by Hospital Treatment Preferences?
Neurocrit Care. 2022 Jun;36(3):846-856.

Gantner D, Wiegers E, .., **Van Essen TA**, et al. Decompressive craniectomy practice following traumatic brain injury, in comparison with randomized trials.
J Neurotrauma. 2022 Jun;39(11-12):860-869

Kals M, Kunzmann K, .., **Van Essen TA**, et al. A genome-wide association study of outcome from traumatic brain injury.
EBioMedicine. 2022 Mar;77:103933.

Theakstone AG, Brennan PM, .., **Van Essen TA**, et al. Vibrational Spectroscopy for the Triage of Traumatic Brain Injury Computed Tomography Priority and Hospital Admissions.
J Neurotrauma. 2022 Jun;39(11-12):773-783.

Galimberti S, Graziano F, .., **Van Essen TA**, et al. CENTER-TBI and TRACK-TBI participants and investigators. Effect of frailty on 6-month outcome after traumatic brain injury: a multicentre cohort study with external validation.
The Lancet Neurol. 2022 Feb;21(2):153-162.

Böhm JK, Schaeben V, .., **Van Essen TA**, et al. Extended Coagulation Profiling in Isolated Traumatic Brain Injury: A CENTER-TBI Analysis.
Neurocrit Care. 2022 Jun;36(3):927-941.

Horton L, Rhodes J, .., **Van Essen TA**, et al. Questionnaires vs Interviews for the Assessment of Global Functional Outcomes After Traumatic Brain Injury.
JAMA Netw Open. 2021 Nov 1;4(11):e2134121.

Sewalt CA, Gravesteijn BY, .., **Van Essen TA**, et al. Primary versus early secondary referral to a specialized neurotrauma center in patients with moderate/severe traumatic brain injury: a CENTER TBI study.
Scand J Trauma Resusc Emerg Med. 2021 Aug 4;29(1):113.

Van Veen E, Van der Jagt M, .., **Van Essen TA**, et al. Occurrence and timing of withdrawal of life-sustaining measures in traumatic brain injury patients: a CENTER-TBI study.
Intensive Care Med. 2021 Oct;47(10):1115-1129.

Citerio G, Robba C, R.., **Van Essen TA**, et al. Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study.
Intensive Care Med. 2021 Sep;47(9):961-973.

Yuh EL, Jain S, .., **Van Essen TA**, et al. Pathological Computed Tomography Features Associated With Adverse Outcomes After
Mild Traumatic Brain Injury: A TRACK-TBI Study With External Validation in CENTER-TBI.
JAMA Neurol. 2021 Sep 1;78(9):1137-1148.

Huijben JA, Dixit A, Stocchetti N, .., **Van Essen TA**, et al. Use and impact of high intensity treatments in patients with traumatic brain injury across Europe: a CENTER-TBI analysis.
Crit Care. 2021 Feb 23;25(1):78.

Van Erp IAM, **Van Essen TA**, Fluiter K, et al. Safety and efficacy of C1-inhibitor in traumatic brain injury (CIAO@TBI): study protocol for a randomized, placebo-controlled, multi-center trial.
Trials. 2021 Dec 4;22(1):874.

Van Praag DLG, Wouters K, .., **Van Essen TA**, et al. Neurocognitive correlates of probable posttraumatic stress disorder following traumatic brain injury.
Brain Spine. 2021 Dec 22;2:100854.

Peppel LD, Heijenbrok-Kal MH, **Van Essen TA**, et al. A delphi procedure on rehabilitation outcome for patients with moderate to severe traumatic brain injury; first phase of the Neurotraumatology Quality Registry (Net-QuRe).
J Rehabil Med. 2022 Jan 11;54:jrm00249.

Huie JR, Mondello S, .., **Van Essen TA**, et al. Biomarkers for Traumatic Brain Injury: Data Standards and Statistical Considerations.
J Neurotrauma. 2021 Sep 15;38(18):2514-2529.

Wiegers EJA, Lingsma HF, .., **Van Essen TA**, et al. Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study.
The Lancet Neurol. 2021 Aug;20(8):627-638.

Gravesteijn BY, Sewalt CA, Venema E, .., **Van Essen TA**, et al. Missing Data in Prediction Research: A Five-Step Approach for Multiple Imputation, Illustrated in the CENTER-TBI Study.
J Neurotrauma. 2021 Jun 1;38(13):1842-1857.

Böhm JK, Güting H, Thorn S, .., **Van Essen TA**, et al. Global Characterisation of Coagulopathy in Isolated Traumatic Brain Injury (iTBI): A CENTER-TBI Analysis.
Neurocrit Care. 2021 Aug;35(1):184-196.

Mikolić A, Polinder S, .., **Van Essen TA**, et al. Prediction of Global Functional Outcome and Post-Concussive Symptoms after Mild Traumatic Brain Injury: External Validation of Prognostic Models in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study.
J Neurotrauma. 2021 Jan 15;38(2):196-209.

Mikolić A, Van Klaveren D, .., **Van Essen TA**, et al. Differences between Men and Women in Treatment and Outcome after Traumatic Brain Injury.
J Neurotrauma. 2021 Jan 15;38(2):235-251.

Jacob L, Cogné M, .., **Van Essen TA**, et al. Predictors of Access to Rehabilitation in the Year Following Traumatic Brain Injury: A European Prospective and Multicenter Study.
Neurorehabil Neural Repair. 2020 Sep;34(9):814-830.

Timmers M, van Dijck JTJM, .., **Van Essen TA**, et al. How do 66 European institutional review boards approve one protocol for an international prospective observational study on traumatic brain injury? Experiences from the CENTER-TBI study.
BMC Med Ethics. 2020 May 12;21(1):36.

*** Van Essen TA**, Menon DK, Lingsma HF. Unmeasured Confounding in Observational Studies of Management of Cerebellar Intracranial Hemorrhage.
JAMA. 2020 Feb 18;323(7):665-666.

Gravesteijn BY, Sewalt CA, .., **Van Essen TA**, et al. Tracheal intubation in traumatic brain injury: a multicentre prospective observational study.
Br J Anaesth. 2020 Oct;125(4):505-517.

Robba C, Rebora P, .., **Van Essen TA**, et al. Incidence, Risk Factors, and Effects on Outcome of Ventilator-Associated Pneumonia in Patients With Traumatic Brain Injury: Analysis of a Large, Multicenter, Prospective, Observational Longitudinal Study.
Chest. 2020 Dec;158(6):2292-2303.

Van Wijk RPJ, Van Dijck JTJM, .., **Van Essen TA**, et al. Informed consent procedures in patients with an acute inability to provide informed consent: Policy and practice in the CENTER-TBI study.
J Crit Care. 2020 Oct;59:6-15.

Mathieu F, Güting H, .., **Van Essen TA**. Impact of Antithrombotic Agents on Radiological Lesion Progression in Acute Traumatic Brain Injury: A CENTER-TBI Propensity-Matched Cohort Analysis.
J Neurotrauma. 2020 Oct 1;37(19):2069-2080.

Gravesteijn BY, Nieboer D, .., **Van Essen TA**, et al. Machine learning algorithms performed no better than regression models for prognostication in traumatic brain injury.
J Clin Epidemiol. 2020 Jun;122:95-107.

Feng J, Van Veen E, .., **Van Essen TA**, et al. Comparison of Care System and Treatment Approaches for Patients with Traumatic Brain Injury in China versus Europe: A CENTER-TBI Survey Study.
J Neurotrauma. 2020 Aug 15;37(16):1806-1817.

Huijben JA, Wiegers EJA, .., **Van Essen TA**, et al. Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis.
Intensive Care Med. 2020 May;46(5):995-1004.

Huijben JA, Wiegers EJA, .., **Van Essen TA**, et al. Quality indicators for patients with traumatic brain injury in European intensive care units: a CENTER-TBI study.
Crit Care. 2020 Mar 4;24(1):78.

Robba C, Galimberti S, .., **Van Essen TA**, et al. Tracheostomy practice and timing in traumatic brain-injured patients: a CENTER-TBI study.
Intensive Care Med. 2020 May;46(5):983-994.

Vande Vyvere T, De La Rosa E, .., **Van Essen TA**, et al. Prognostic Validation of the NINDS Common Data Elements for the Radiologic Reporting of Acute Traumatic Brain Injuries: A CENTER-TBI Study.
J Neurotrauma. 2020 Jun 1;37(11):1269-1282.

Gravesteijn BY, Sewalt CA, .., **Van Essen TA**, et al. Toward a New Multi-Dimensional Classification of Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research for Traumatic Brain Injury Study.
J Neurotrauma. 2020 Apr 1;37(7):1002-1010.

Zeiler FA, Aries M, .., **Van Essen TA**, et al. Statistical Cerebrovascular Reactivity Signal Properties after Secondary Decompressive Craniectomy in Traumatic Brain Injury: A CENTER-TBI Pilot Analysis.
J Neurotrauma. 2020 Jun 1;37(11):1306-1314.

Van Essen TA, van Gent JAN, Bos MHA, et al. Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis.
Acta Neurochir (Wien). 2020 Feb;162(2):329-336.

*** Van Essen TA**, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and NeT-QuRe.
BMJ Open. 2019 Oct 16;9(10):e033513.

Steyerberg EW, Wiegers E, .., **Van Essen TA**, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study.
The Lancet Neurol. 2019 Oct;18(10):923-934.

Van Dijck JTJM, **Van Essen TA**, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox?
Acta Neurochir (Wien). 2019 May;161(5):875-884.

*** Van Essen TA**, Den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study.
Acta Neurochir (Wien). 2019 Mar;161(3):435-449.

*** Van Essen TA**, Dijkman MD, Cnossen MC, et al. Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma in an Aging Population.
J Neurotrauma. 2019 Apr 1;36(7):1184-1191.

Van Veen E, Van der Jagt M, .., **Van Essen TA**, et al. Brain death and postmortem organ donation: report of a questionnaire from the CENTER-TBI study.
Crit Care. 2018 Nov 16;22(1):306.

Vande Vyvere T, Wilms G, .., **Van Essen TA**, et al. Central versus Local Radiological Reading of Acute ComputedTomography Characteristics in Multi-Center Traumatic Brain Injury Research.
J Neurotrauma. 2019 Apr 1;36(7):1080-1092.

Huijben JA, Van der Jagt M, .., **Van Essen TA**, et al. Variation in Blood Transfusion and Coagulation Management in Traumatic Brain Injury at the Intensive Care Unit: A Survey in 66 Neurotrauma Centers Participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Study.
J Neurotrauma. 2018 Jan 15;35(2):323-332.

* Cnossen MC, **Van Essen TA**, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury.
Clin Epidemiol. 2018 Jul 18.

Huijben JA, Volovici V, .., **Van Essen TA**, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.
Crit Care. 2018 Apr 13;22(1):90.

Van Essen TA, De Ruiter GCW, Den Boogert HF, et al. Surgical dilemmas in traumatic brain injury
Tijdschr Neurol Neurochir 2018;119(2):46-51)

Van Dijck JT, Reith FC, .., **Van Essen TA**, et al. Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management.
J Neurosurg Sci. 2018 Apr;62(2):153-177.

* Maas AIR, Menon DK, .., **Van Essen TA**, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research.
The Lancet Neurol. 2017 Dec;16(12): 987-1048.

Cnossen MC, Huijben JA, .., **Van Essen T**, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study.
Crit Care. 2017 Sep 6;21(1):233.

*** Van Essen TA**, De Ruiter GC, Kho KH, et al. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands.
J Neurotrauma. 2017 Feb 15;34(4):881-889.

Van Essen TA, Van Rijswijk JB. 'Intranasal toothache': case report.
J Laryngol Otol. 2013 Mar;127(3):321-2.

Van Essen TA, Van der Giessen RS, Koekkoek SK, et al. Anti-malaria drug mefloquine induces motor learning deficits in humans.
Front Neurosci. 2010 Nov 19;4:191.

Van Essen TA, Heeringa JJ, Muizelaar JP. (In)appropriate neurosurgical consultation. *Clin Neurol Neurosurg. 2010 Nov;112(9):775-80*

PRESENTATIONS

Invited

Effectiveness of surgery in acute subdural hematoma - Henk Verbiest price 2022
Plenary presentation, Wintermeeting 2022, November 25, *Nederlandse Vereniging voor Neurochirurgie* (NVvN, yearly scientific meeting of the Dutch Neurosurgical Society) Rotterdam, The Netherlands

Clustering of ICU treatment strategies in traumatic brain injury.
Presentation, European Association of Neurological Societies (EANS) 2022, 19 October, Belgrade, Serbia

Surgical practice variation in traumatic acute subdural hematoma.
European Society of Intensive Medicine/EANS 2022, 16 October, Belgrade, Serbia

Evidence of surgical evacuation in traumatic acute subdural hematoma
INTS (International Neurotrauma Society) 2022, 19 August, Berlin, Germany

TBI in the elderly; Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma (RESET-ASDH trial)
EANS webinar, 25 May 2022

Comparative effectiveness research – a case study in acute subdural hematoma
EANS webinar, 28 April 2021

Variation in neurosurgical management of traumatic brain injury
Nordic Neurotrauma Conference 2019, 19 November, Lund, Sweden

Effectiviteit van chirurgie voor het traumatisch acuut subduraal hematoom
Hoelendag 2018, The Hague, The Netherlands

Other

Comparative effectiveness of surgery in traumatic acute subdural hematoma.
Presentation, EANS 2022, 18 October, Belgrade, Serbia

Comparative effectiveness of surgery in traumatic acute subdural hematoma
Plenary presentation, INTS (International Neurotrauma Society) 2022 Berlin, 19 August 2022, Berlin, Germany

Functional outcome after surgical or conservative treatment of acute subdural hematoma: a living systematic review
Presentation, EANS 2019, 17 September, Dublin, Ireland

Randomized Evaluation of Surgery in Elderly with a Traumatic Acute Subdural Hematoma (RESET-ASDH): protocol of a pragmatic randomized controlled trial
Poster presentation, EANS 2019, Dublin, Ireland

The Dutch Neurotraumatology Quality Registry
Poster presentation, INTS 2018, Toronto, Canada

Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study
Poster presentation, INTS 2018, Toronto, Canada

Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population
Plenary presentation, INTS 2016, 3 February, Capetown, South-Africa.

The mortality reduction of acute surgery in traumatic acute subdural hematoma since the 19th century: systematic review and meta-analysis with dramatic effect - is surgery the obvious parachute?
Poster presentation, INTS 2016, Capetown, South-Africa.

Comparative effectiveness of surgery in traumatic acute subdural and intracerebral hematoma: study protocol for an observational study
Presentation, International Brain Injury Association (IBIA) 2016, 2 March 2016, The Hague, The Netherlands

Factors of influence on surgical decision making for traumatic acute subdural hematoma
Plenary presentation, INTS 2014, Budapest, Hungary

Treatment variation for traumatic acute subdural hematoma
Poster presentation, INTS 2014, Budapest, Hungary

'*Wel of niet opereren bij het traumatisch acuut subduraal hematoom?*'
Plenary presentation, Wintermeeting 2014 NVvN Utrecht, The Netherlands

Factors of influence on surgical decision making for traumatic acute subdural hematoma
Poster presentation, Medical Center Haaglanden conference 2013, The Hague, The Netherlands

Treatment variation for traumatic acute subdural hematoma
Poster presentation, Medical Center Haaglanden conference 2013, The Hague, The Netherlands

NON-REFEREED ARTICLES AND PUBLIC (NEWS)ITEMS
***Federatie Medisch Specialisten* (Dutch federation of medical specialists) press release: nomination *Wetenschaps- en innovatieprijs 2023* (Science and Innovation prize 2023) on behave of the NVvN.**
2 March 2023
https://demedischspecialist.nl/voordracht-2023-neurochirurgie

Leiden University Medical Center (LUMC) press release: '*Spoedoperatie bij bloeding onder hersenvlies onderzocht*'
6 May 2022
https://www.lumc.nl/over-het-lumc/nieuws/2022/Mei/spoedoperatie-bij-bloeding-niet-altijd-nodig/

News item '*Spoedoperatie bij bloeding onder hersenvlies soms overbodig*'
Article, *Medisch Contact,* Number 20, 19 May 2022
Medisch Contact online press release: '*Spoedoperatie bij bloeding onder hersenvlies soms overbodig'*
10 May 2022
https://www.medischcontact.nl/nieuws/laatste-nieuws/nieuwsartikel/spoedoperatie-bij-bloeding-onder-hersenvlies-soms-overbodig.htm

Van Essen TA, Peul WC. Current evidence base for neurosurgery in traumatic brain injury.
Course book. Biemond course for residents neurology, July 2020.

Dutch newspaper *De Volkskrant* article, Ellen de Visser: '*Die Ene Patient', "Lange tijd had ik een rubberen ziel, dankzij Pieter ben ik empathischer geworden."*
9 September 2017
https://www.volkskrant.nl/wetenschap/lange-tijd-had-ik-een-rubberen-ziel-dankzij-pieter-ben-ik-empathischer-geworden~bbbcef19/

LUMC press release: '*Welke behandeling is het best bij hersenletsel?*' 2015
https://www.lumc.nl/org/sips/onderzoeken/lopende-onderzoeken/CENTER-TBIenNet-QuRe

Conference of the University Neurosurgical Center Holland: '*Neurotrauma in de regio*'
28 June 2015

PROSPERO International prospective register of systematic reviews: Systematic review and meta-analysis of the treatment in traumatic acute subdural hematoma in terms of 1) mortality and 2) functional outcome. PROSPERO registration numbers CRD42015025491 and CRD42019125336.

GRANTS AND AWARDS
Nomination *Wetenschaps- en innovatieprijs 2023* (Science and Innovation prize 2023) of the *Federatie Medisch Specialisten* (Dutch federation of medical specialists)
2 March 2023

Niels Stensen fellow 2023, 58.000 euro

Henk Verbiest prize 2022, NVvN 1250 euro

Co-applicant Randomized Evaluation of Surgery in Elderly with Traumatic Acute Subdural Hematomas (RESET-ASDH), 2020, The Netherlands Organisation for Health Research and Development (Benefit, ZonMW), 1.800.000 euro

Co-applicant 'Complement Inhibition: Attacking Overshooting inflammation @ fter Traumatic Brain Injury (CIAO-TBI)'), 2020, De Hersenstichting, (Dutch Brain Foundation) and Takeda Pharmaceutical Company, 900.000 euro

Personal scholarship within the FP7 program, 2019, European Union, 8000 euro

Co-applicant 'Program Grant TBI', 2014, for NeuroTraumatology Quality Registry (Net-QuRe), *De Hersenstichting* (Dutch Brain Foundation), 600.000 euro

Travel award International Neurotrauma Society 2014, Budapest, Hungary, 1500 euro

CURRICULUM VITAE

Thomas van Essen was born on July 29, 1985 in Rotterdam, The Netherlands. He obtained his high school Gymnasium diploma at the *Erasmiaans Gymnasium* in Rotterdam in June 2003. In September he started the study Applied Physics at the Technical University Delft where he successfully concluded his propaedeutic exam. During the bachelor program in Delft he started the master of science program Neuroscience at the Erasmus University Rotterdam. It was here that, despite his affinity with physics, he decided to pursue a different career. Therefore, in august 2005 he entered medical school at the Erasmus University. In July 2012 he received his medical degree (cum laude) and his Master of Science in neuroscience at the department of Neuroscience (under the supervision of dr. De Jeu and Prof. De Zeeuw). During his studies he successfully competed at an international level of crew rowing until 2009, after which he played football at an amateur - but highly ambitious - level.

A scientific internship for his bachelor thesis at the University of California Davis (prof. Muizelaar) sowed the seed of his interest in acute neurosurgery and related research. Therefore, in November 2012 he started as a resident neurosurgery not in training at Haaglanden Medical Center and Leiden University Medical Center (dr. Nandoe Tewarie, dr. Walchenbach, dr. Koot and prof. Peul). At the job interview he put forward the research questions of this thesis, after which he successful applied for a grant of the Dutch Brain Foundation (*Hersenstichting Nederland*).
In July 2014 he started as a PhD graduate neurosurgery and epidemiology (prof. Peul and prof. Rosendaal). He received a personal scholarship within the FP7 program (European Union, 2019). Thomas presented his research at several (inter)national meetings. He was invited to give a plenary lecture on the effectiveness of acute surgery in acute subdural hematoma at the biennial International Neurotrauma Society Berlin meeting. Furthermore, he won the annual Henk Verbiest prize of the Dutch Neurosurgical Society for best article in 2022, and his study was nominated for the *Wetenschaps- en innovatieprijs 2023* (Science and Innovation prize 2023) of the *Federatie Medisch Specialisten* (Dutch federation of medical specialists).

In March 2016, Thomas started his neurosurgical training that he finished in October 2022. He was awarded a personal grant (Niels Stensen Fellowship) to pursue experience at a top university or institute abroad. In 2023 he started as an Honorary Fellow at the Division of Neurosurgery of the University of Cambridge (prof. Hutchinson) to work as a neurosurgeon and post-doc researcher. In addition, he worked at the Department of Neurological Surgery of the University of California San Francisco (prof. Manley) as a visiting fellow from November 2022 untill February

2023. Both fellowships have the scientific aim to study treatment effect heterogeneity of surgery in traumatic brain injury.
These fellowships will be followed by a fellowship functional neurosurgery at Dalhousie University (dr. Weise and prof. Clarke, Halifax, Nova Scotia, Canada).

Thomas lives together with Chrisje den Besten, their 2-year-old son Philip and their newborn son Floris.

Den Haag, Leiden
2023