ACUTE MANAGEMENT OF MINOR HEAD INJURY

KELLY FOKS

Acute Management of Minor Head Injury

Kelly Alexandra Foks

ISBN: 978-94-6380-635-0

This thesis is partly realized due to the financial support of the Erasmus University Rotterdam and the Department of Public Health, Erasmus MC.

Cover design by Bregje Jaspers and printing by Proefschriftmaken.nl

Acute Management of Minor Head Injury

Acute diagnostiek en behandeling van licht traumatisch hersenletsel

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof. dr. R.C.M.E. Engels
en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 18 december 2019 om 11.30 uur

door

Kelly Alexandra Foks

geboren op vrijdag 25 december 1987

te Voorburg

Erasmus University Rotterdam

Promotiecommissie

Promotoren:	Prof.dr. D.W.J. Dippel Prof.dr. E.W. Steyerberg
Overige leden:	Prof.dr. M. Smits Prof.dr. J. van der Naalt Prof.dr. A. Algra
Copromotoren:	Dr. S. Polinder Dr. H.F. Lingsma

Table of contents

Chapter 1

General introduction

Traumatic brain injury

Head injury or traumatic brain injury (TBI) is a common injury with at least 2.5 million new cases each year in Europe and 3.5 million in the USA.[1] TBI is estimated to contribute 37% of the injury mortality in Europe.[2] The epidemiology of TBI is changing; a higher incidence of falls and older patients is described in high income countries, while the incidence of road traffic accidents is increasing in low income countries.[1,3] Due to the history of the patient, complexity of the brain and pattern and extend of the injury TBI is a heterogeneous disease, which leads to a wide variation in clinical practice.

Most head injury patients (~90%) have mild TBI or minor head injury (MHI).[4] In the Netherlands an estimated 45.000 MHI patients are seen at the emergency departments annually.[5] Because not all patients with MHI are referred to a hospital for evaluation the incidence is likely to be higher.

The definition jungle: minor head injury and mild traumatic brain injury

For patients with minor injury several definitions are used interchangeably such as MHI, mild TBI, concussion, mild head injury, and minor traumatic brain injury.[6-8] MHI and mild TBI are used most often. MHI is usually used for patients with blunt injury to the head including those patients with a head laceration (i.e. a skin cut or tear) or bruise. The definition mild TBI is used for patients with a significant injury to the head and often the presence of loss of consciousness for less than 30 minutes and/or the presence of post-traumatic amnesia for less than 24 hours is warranted. In this thesis, I will use these two concepts as defined here.

Management at the emergency department

When a patient with MHI or mild TBI arrives at the emergency department a clinical assessment by the attending physician is usually performed. Physicians will ask the patient about the injury mechanism, current symptoms, patient history, and perform a neurological examination. The Glasgow Coma Scale (GCS) is used to categorize head injury patients at presentation in the hospital (Table 1).[9,10] The GCS measures the level of consciousness and categorizes the patients based on severity of symptoms. Responses in three domains (eye, motor, verbal) are assessed and the domain scores are added to give the total GCS score.[9]

Table 1. Glasgow Coma Scale

Eye opening	Motor response	Verbal response
1 = no response	1 = no response	1 = no response
2 = to pain	2 = extension	2 = incomprehensible speech
3 = to speech	3 = abnormal flexion to pain	3 = inappropriate speech
4 = spontaneous	4 = normal flexion to pain	4 = confused conversation
	5 = localizes pain	5 = orientated
	6 = obeys commands	

Patients with a GCS total score between 13 and 15 have mild TBI or MHI. Patients with a lower GCS score have moderate TBI (GCS total score 9-12) or severe TBI (GCS total score 3-8).

After the clinical assessment often a computed tomography (CT) scan of the head is performed. Less than 10% of all MHI patients have traumatic (intra)cranial findings on a head CT scan (Figure 1). These findings are mainly small contusions, traumatic subarachnoid hemorrhages and linear skull fractures. However, less than 1% of patients have more serious findings such as a depressed skull fracture or epidural hematoma and need a neurosurgical intervention.[11,12]

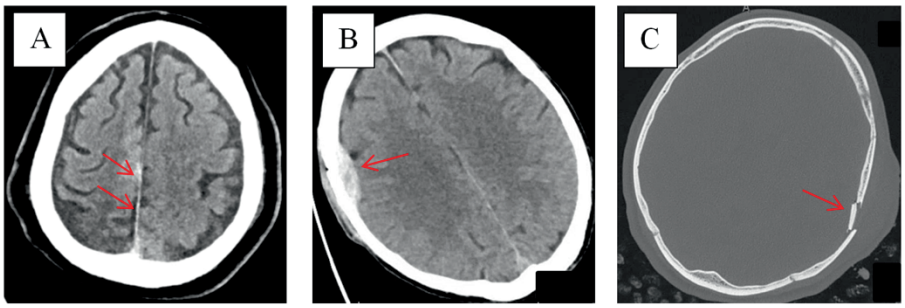


Figure 1. Example traumatic intracranial CT findings
A. small subdural hematoma (located at the falx cerebri), B. epidural hematoma (located right frontal hemisphere), C. depressed skull fracture (located on the left side of the skull).
Source: head CTs from MHI patients in the dataset used in this thesis

After the diagnostic tests, the physician needs to decide if the patient should be admitted to the hospital or could be discharged home. This decision is mostly based on the result of the head CT.[13] If a patient with a normal head CT has no other injuries or reasons for admission, such as non-accidental injury or intoxication with alcohol or drugs, discharge to home is usually considered safe.[14] Patients with traumatic intracranial finding(s) on CT are mostly recommended to be admitted to the hospital for observation, however many controversies exist in the admission policies. Should the patients be admitted to a special neurology ward, or is an intensive care unit admission necessary for neurological observation? Should patients with small hematomas be discharged home? In case of non-neurosurgical centers, do all patients with traumatic findings need to be transferred to the nearest neurosurgical center?

Controversies exist also in discharge policies and follow-up care. About 15-25% of MHI patients have long-term post-traumatic symptoms, such as headache, dizziness, fatigue, memory and concentration problems months after the injury.[15,16] Some evidence exists, that early interventions could reduce these post-traumatic symptoms.[17,18] Examples of early interventions are handing out information about the risks after MHI when the patient is discharged home and scheduling routine follow-

up sessions. However, there are also studies that found no effect of these early intervention strategies.[19,20]

Vascular traumatic injury

Besides brain injury, patients with traumatic head or neck injuries are also at risk of blunt cerebrovascular injuries (BCVI), involving trauma to the carotid and vertebral arteries.[21] The reported incidence of BCVI is much lower than TBI and estimated at 0.1-2.7%.[22,23] However, the complications of BCVI such as ischemic strokes and death are more severe. BCVI is caused by severe hyperextension or rotation, a direct blow to the artery or laceration by an adjacent bone fracture. The injury to the artery can range from mild to complete transection. Disruption of the arterial wall may cause local thrombus formation and subsequent thromboembolism. Furthermore, complete occlusion or transection of the artery can lead to stroke through decreased cerebral blood flow.

Computed tomography angiography (CTA) is nowadays used to identify patients with BCVI.[24,25] However, which TBI patients need screening with CTA and optimal treatment in BCVI is often debated.

CT decision rules

Because of the low risk of traumatic intracranial findings in patients with MHI, not all patients need a head CT. Therefore, CT decision rules and clinical guidelines have been developed to help physicians decide which patients are at risk of intracranial complications and need a head CT. Based on the findings of the clinical assessment at the emergency department the decision rule or clinical guideline will lead to a recommendation for CT scanning. Examples of CT decision rules and clinical guidelines are the New Orleans Criteria (NOC), Canadian CT Head Rule (CCHR), CT in Head Injury Patients (CHIP) rule, European Federation of Neurological Societies (EFNS) TBI guideline, National Institute for Health and Care Excellence (NICE) guideline for head injury and Scandinavian guidelines for TBI.[11,12,14,26-28] For example the CHIP rule consists of major and minor criteria; all patients with at least 1 major criterion or 2 minor criteria have an increased risk of intracranial complications and should undergo a head CT (Table 2). All rules and guidelines use somewhat different risk factors leading to variation in CT scanning, where one rule will recommend to perform a head CT and the other will not. The common goal of the rules and guidelines is to identify all patients with serious findings and to prevent unnecessary CT scans at the emergency department. Unnecessary CT scans lead to higher costs, longer waiting times at the emergency department and unnecessary radiation risks. The CHIP rule is currently implemented in the Dutch national guideline for MHI, however the CHIP rule was never externally validated and the

question remains how the CHIP rule performs compared to other diagnostic decision rules.

Table 2. CHIP prediction rule

CT indicated in the presence of ≥ 1 major criterion	CT indicated in the presence of ≥ 2 minor criteria
Pedestrian or cyclist versus vehicle	Fall from any elevation
Ejected from vehicle	Persistent anterograde amnesia**
Vomiting	Posttraumatic amnesia of 2-4 hours
Post-traumatic amnesia 4 hours or more	Contusion of skull
Clinical sign of skull fracture*	Neurologic deficit
GCS score < 15	Loss of consciousness
GCS deterioration 2 or more points (1hr after presentation)	GCS deterioration of 1 point (1 hour after presentation)
Use of anticoagulant therapy	Age 40-60 years
Posttraumatic seizure	
Age 60 years or older	

CT = computed tomography, GCS = Glasgow Coma Scale
* for example leakage of cerebrospinal fluid, raccoon eyes, bleeding from the ear
** any deficit of short-term memory

Aim of this thesis

Because of the high incidence and associated long-term complications MHI is a major socioeconomic and health burden throughout the world. Improving the management for MHI and improving the CT decision rules could lead to a more cost-effective and safe TBI care.

The overall aim of my thesis is to describe and improve the acute management of MHI. To address this aim I want to answer the following questions:

1. What is the extent of practice variation in management of patients with MHI and mild TBI at the emergency department?
2. How can the CT decision rules for MHI be improved?

Data sources

Currently, a large multicenter prospective study in Europe, the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, is being conducted to improve characterization, classification and to identify best clinical care by using comparative effectiveness care.[29] Not only in Europe, but also in the USA (Transforming Research and Clinical Knowledge in Traumatic Brain Injury, TRACK-TBI), China and India, and for pediatrics large multicenter trials have started to optimize TBI care. To answer the first question of this thesis I used the CENTER-TBI dataset as well as two single-center retrospective datasets. For the second question I created in a collaborative effort the CHIP Refinement Study (CREST) dataset, a large Dutch multicenter MHI study.

Outline of this thesis

The thesis consists of two parts. In the first part (**Chapter 2-5**) I investigated the variation in management of MHI at the emergency department. **Chapter 2** provides an overview of the management of mTBI at the emergency department and hospital admission in Europe based on questionnaire surveys. In **Chapter 3** the practice variation in management of mTBI patients after emergency department presentation in Europe is described. The impact of MHI guidelines on the use of CT over two decades is examined in **Chapter 4**. The use and clinical consequences of CTA in patients with BCVI is described in **Chapter 5**.

In the second part of this thesis (**Chapter 6-8**) I focused on improving the CT decision rules. In **Chapter 6** the results of an external validation study of frequently used CT decision rules for MHI in a prospective, multicenter cohort study in the Netherlands are described. **Chapter 7** studies the role of loss of consciousness and posttraumatic amnesia on the risk of intracranial complications in MHI. Lastly, in **Chapter 8** an update of the CHIP prediction rule is performed.

The main results of the preceding chapters in this thesis will be summarized and discussed in **Chapter 9**.

References

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017;16(12):987-1048.
2. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. Lancet Public Health 2016;1(2):e76-e83.
3. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol 2013;9(4):231-6.
4. Feigin VL, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. Lancet Neurol 2013;12(1):53-64.
5. Van den Brand CL, Karger LB, Nijman ST, et al. Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. Eur J Emerg Med 2017.
6. Carroll LJ, Cassidy JD, Holm L, et al. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004(43 Suppl):113-25.
7. Kristman VL, Borg J, Godbolt AK, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95(3 Suppl):S265-77.
8. Shukla D, Devi BI. Mild traumatic brain injuries in adults. J Neurosci Rural Pract 2010;1(2):82-8.
9. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2(7872):81-4.
10. Teasdale G, Maas A, Lecky F, et al. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol 2014;13(8):844-54.
11. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet 2001;357(9266):1391-6.
12. Smits M, Dippel DW, Steyerberg EW, et al. Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med 2007;146(6):397-405.
13. af Geijerstam JL, Oredsson S, Britton M, et al. Medical outcome after immediate computed tomography or admission for observation in patients with mild head injury: randomised controlled trial. Bmj 2006;333(7566):465.
14. National Clinical Guideline C. National Clinical Guidance Centre. (2014). CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults. . National Institute for Health and Care Excellence 2014.
15. Ponsford J, Nguyen S, Downing M, et al. Factors associated with persistent post-concussion symptoms following mild traumatic brain injury in adults. J Rehabil Med 2018.
16. Carroll LJ, Cassidy JD, Peloso PM, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004(43 Suppl):84-105.
17. Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome following mild head injury in adults. J Neurol Neurosurg Psychiatry 2002;73(3):330-2.
18. Nygren-de Boussard C, Holm LW, Cancelliere C, et al. Nonsurgical interventions after mild traumatic brain injury: a systematic review. Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95(3 Suppl):S257-64.
19. Gravel J, D'Angelo A, Carriere B, et al. Interventions provided in the acute phase for mild traumatic brain injury: a systematic review. Syst Rev 2013;2:63.
20. Matuseviciene G, Eriksson G, DeBoussard CN. No effect of an early intervention after mild traumatic brain injury on activity and participation: A randomized controlled trial. J Rehabil Med 2016;48(1):19-26.

21. Burlew CC, Biffl WL. Blunt cerebrovascular trauma. Curr Opin Crit Care 2010;16(6):587-95.
22. Miller PR, Fabian TC, Croce MA, et al. Prospective screening for blunt cerebrovascular injuries: analysis of diagnostic modalities and outcomes. Ann Surg 2002;236(3):386-93; discussion 93-5.
23. Franz RW, Willette PA, Wood MJ, et al. A systematic review and meta-analysis of diagnostic screening criteria for blunt cerebrovascular injuries. J Am Coll Surg 2012;214(3):313-27.
24. Roberts DJ, Chaubey VP, Zygun DA, et al. Diagnostic accuracy of computed tomographic angiography for blunt cerebrovascular injury detection in trauma patients: a systematic review and meta-analysis. Ann Surg 2013;257(4):621-32.
25. Foreman PM, Harrigan MR. Blunt Traumatic Extracranial Cerebrovascular Injury and Ischemic Stroke. Cerebrovasc Dis Extra 2017;7(1):72-83.
26. Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. N Engl J Med 2000;343(2):100-5.
27. Vos PE, Alekseenko Y, Battistin L, et al. Mild traumatic brain injury. Eur J Neurol 2012;19(2):191-8.
28. Unden J, Ingebrigtsen T, Romner B, et al. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 2013;11:50.
29. 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.

Part 1

Practice variation in minor head injury management

Chapter 2

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

Kelly A. Foks
Maryse C. Cnossen
Diederik W.J. Dippel
Andrew Maas
David Menon
Joukje van der Naalt
Ewout W. Steyerberg
Hester Lingsma
Suzanne Polinder
CENTER-TBI investigators and participants

Abstract

Previous studies have indicated that there is no consensus about management of mild traumatic brain injury (mTBI) at the emergency department (ED) and during hospital admission. We aim to study variability between management policies for TBI patients at the ED and at the hospital ward across Europe. Centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study received questionnaires about different phases of TBI care. These questionnaires included 71 questions about TBI management at the ED and at the hospital ward. We found differences in how centers defined mTBI. For example, 40 centers (59%) defined mTBI as a Glasgow Coma Scale (GCS) score between 13 and 15 and 26 (38%) defined it as a GCS score between 14 and 15. At the ED various guidelines for the use of head computed tomography (CT) in mTBI patients were used; 32 centers (49%) used national guidelines, 10 centers (15%) local guidelines, and 14 centers (21%) used no guidelines at all. Also, differences in indication for admission between centers were found. After ED discharge, 7 centers (10%) scheduled a routine follow-up appointment, whereas 38 (54%) did so only after ward admission. In conclusion, large between-center variation exists in policies for diagnostics, admission, and discharge decisions in patients with mTBI at the ED and in the hospital. Guidelines are not always operational in centers, and reported policies systematically diverge from what is recommended in those guidelines. The results of this study may be useful in the understanding of mTBI care in Europe and show the need for further studies on the effectiveness of different policies on outcome.

Introduction

Traumatic brain injury (TBI) is a common reason for presentation at the emergency department (ED) and hospital admission in Europe.[1] A recent systematic review estimated the number of annual hospital admissions at 262 per 100,000 persons.[2] However, many more patients are seen at the ED each year. TBI is associated with significant long-term disability and has become a major socioeconomic and health burden throughout the world.

Among the patients with TBI presenting at the ED, the large majority (75–90%) are classified as having "mild" TBI (mTBI). The most frequently used definition of mTBI is a Glasgow Coma Scale (GCS) score between 13 and 15 and loss of consciousness of less than 30 min or amnesia not extending beyond 24 h after blunt head injury.[3,4] Because of the low risk of intracranial damage, a computed tomography (CT) scan of the head or hospital admission is not always necessary in these patients. To estimate the risk of intracranial abnormalities in mTBI, various prediction rules and guidelines have been developed, for example, the Canadian CT head rule, the National Institute for Health and Care Excellence (NICE) guidelines for head injury, and the CT in Head Injury Patients (CHIP) rule.[5–8] Based on a set of minor and major risk factors, these prediction rules recommend whether a CT scan of the head should be performed. The results of the CT scan subsequently influence the decision on whether a patient should be admitted to the hospital or could be safely discharged home.

After mTBI, patients may experience post-traumatic symptoms such as headaches, dizziness, and memory or concentration problems, resulting in significant disability. In many cases these symptoms dissolve over time; however, a group of patients (estimated at between 5 and 30%) may suffer from prolonged symptoms.[9] Studies have shown that handing out discharge information and scheduling routine follow-up sessions could reduce these post-traumatic symptoms.[10,11]

However, still little is known about the optimal treatment of mTBI and there is no consensus about management of these patients.[12] Therefore, variation in structure and process of mTBI care is expected, which may result in variation in outcome. In this study, we aimed to describe the current management of mTBI at the EDs and hospital wards in Europe. Specifically, we aimed to provide insight in the use of diagnostics, admission policy, and discharge policy at the ED and hospital ward.

Methods

Questionnaires

Between 2014 and 2016, we approached the principal investigators of 71 centers from 19 European countries and Israel, participating in the CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study, a multicenter prospective observational study on TBI, [13] with the

request to complete a set of 11 questionnaires about structure and process of care for TBI patients: The Provider Profiling (PP) questionnaires. The questionnaires were developed based on literature and expert validation and were subsequently pilot-tested. Questionnaires were discussed during presentations, workshops and email conversations. Reliability, which was assessed by calculating concordance rates between duplicate questions (5% of the questions) in all 11 questionnaires, was adequate (median concordance rate of 0.85). More detailed information about the development, administration and content of the total set of provider profiling questionnaires is available in a previous publication.[14]

For this study, we analyzed the results of a questionnaire about ED and a questionnaire about hospital admission policy, for a total of 71 questions (Supplementary Appendix 1; see online supplementary material at htpp://www.liebertpub.com). Topics included structural characteristics of hospital and ED, imaging, guidelines, treatment, admission policy, observation and discharge policy at the ED and in hospital ward.

Question formats and definitions

Most questions had a multiple choice format where one or more answers could be selected. Two questions had an open format. Questions addressed structures (e.g., "Is overnight observation at the ED available for patients with TBI?") and processes (e.g., "Are guidelines or protocols used to decide when mTBI patients are discharged from the ED?"). The questions about processes refer to general policies rather than individual treatment preferences. General policy was defined as the way the majority of patients with a certain indication would be treated (>75%).

Statistical analysis

We used standard descriptive statistics. Categorical variables were presented as frequencies and percentages and continuous variables were presented as medians and interquartile ranges (IQR). Analysis was performed using IBM Statistical Package for Social Sciences (SPSS) version 21.

Results

All 71 centers completed the Hospital admission questionnaire and 68 centers completed the ED questionnaire (response rates 100% and 96%, respectively). Among the centers that did not complete the ED questionnaire, three centers (4%) indicated that their center had no ED because they specialized in severe neurotrauma or collaborated with the ED of another hospital. The questionnaires were answered by ED physicians, neurosurgeons, neurologists, intensivists, and administrative staff members. The majority of participating centers were academic (n = 65; 92%), level 1 trauma centers (n = 48; 68%) situated at an urban location (n = 70; 99%).

Classification of TBI

It appeared that different definitions of severity levels for TBI were used (Table 1). Forty centers (59%) defined mTBI as a GCS score between 13 and 15 and 26 centers (38%) as a GCS score between 14 and 15. Moderate TBI was considered a GCS score between 9 and 12 in 38 centers (56%) and 9 and 13 in 22 (32%). The majority of the centers considered severe TBI as a GCS score between 3 and 8 (n = 62; 91%).

Table 1. GCS scores that are considered as mild, moderate and severe TBI

GCS score	N (%)
Mild TBI	
11-14	1 (1.5%)
12-15	1 (1.5%)
13-15	**40 (59%)**
14-15	26 (38%)
Moderate TBI	
8-11	1 (1.5%)
8-12	2 (3%)
9-12	**38 (56%)**
9-13	22 (32%)
9-14	1 (1.5%)
10-13	1 (1.5%)
11-13	1 (1.5%)
11-14	1 (1.5%)
12-13	1 (1.5%)
Severe TBI	
3-7	1 (1.5%)
3-8	**62 (91%)**
3-9	2 (3%)
3-10	2 (3%)
3-11	1 (1.5%)

The responders were asked to enter the lowest and highest GCS score per TBI group, the bold GCS range represents the range most common in the literature. GCS = Glasgow Coma Scale, TBI = traumatic brain injury

Diagnostics at the ED

ED physicians (n = 35; 49%) and neurosurgeons (n = 15; 21%) were most often in charge of the treatment of TBI patients at the ED. At the ED, various rules or guidelines for the use of head CT in patients with mTBI were used: more than half of the centers used multi-nation guidelines, such as the NICE-guidelines (n = 16; 24%), the Scandinavian guidelines (n = 7; 10%), or other inter-nation guidelines (n = 12; 17%).15 Only a few of the centers used prediction rules such as the Canadian CT Head rule (n = 4; 6%), the New Orleans criteria (n = 1; 1.5%), or the CHIP rule (n = 4; 6%).16 In addition, 10 centers (15%) used other local guidelines and 14 centers (20.5%) used no guidelines at all. More than 90% (n = 62) of the centers considered their CT scanning policy liberal. Most centers (n = 45; 66%) stated they are more restrictive in the use of a CT scan in children compared with adults. CT scans at the ED were mostly ordered by ED physicians (n = 37; 54%) and neurosurgeons (n = 16; 24%). Only in 7% of the centers (n = 5, including 4 centers from The Netherlands) do neurologists order the CT scans. Most centers standardly

perform a CT scan in patients with clinical signs of skull base fracture, any neurological deficit, or a seizure (Fig. 1). In some situations the indication for CT differs among centers. For example, 50 centers (74%) standardly use a CT scan in patients on anticoagulant therapy, whereas 15 (22%) indicated that they would do this often. The CT scanning guidelines were mainly implemented by written protocols and algorithms (n = 38; 56%) or via verbal direction from senior doctors in 22 centers (32%, Supplementary Table 1).

In half of the centers guideline development and maintenance is overseen by multi-disciplinary groups (Supplementary Table 1). The majority of centers have not performed audits to check for adherence to guidelines in the ED (n = 27; 40%; Supplementary Table 1).

Magnetic resonance imaging (MRI) was used in addition to the CT scan if there was discrepancy between clinical symptomatology and presence of CT abnormalities in mTBI patients (75% of the centers). In 6 centers (9%) from Austria, Denmark, Spain, Sweden, and United Kingdom, s100B is routinely determined as a prognostic biomarker for neurological deterioration. Many centers had the availability of overnight observation at the ED for patients with TBI before they were discharged (n = 54; 79%).

Admission at the ward

At the hospital ward, neurosurgeons (n = 56; 79%) were most often in charge of the treatment of TBI patients. Forty-four (65%) centers indicated use of guidelines in the decision on whether mTBI patients should be admitted to the hospital ward. Most centers admitted patients with TBI to the neurosurgical ward (n = 53; 75%). In addition, patients with TBI were routinely admitted to the neurology (n = 16; 23%) or surgery (n = 15; 21%) ward. Patients with cerebrospinal fluid (CSF) leak, CT progression, new CT abnormalities, or shock were standardly admitted to the ward. For other admission indications, the policy was more diverse. For example, 25 centers (37%) indicated that patients with pre-injury anticoagulation were routinely admitted to the ward, whereas 27 centers (39%) indicated that they would only admit these patients to the ward if other risk factors are present (Fig. 2).

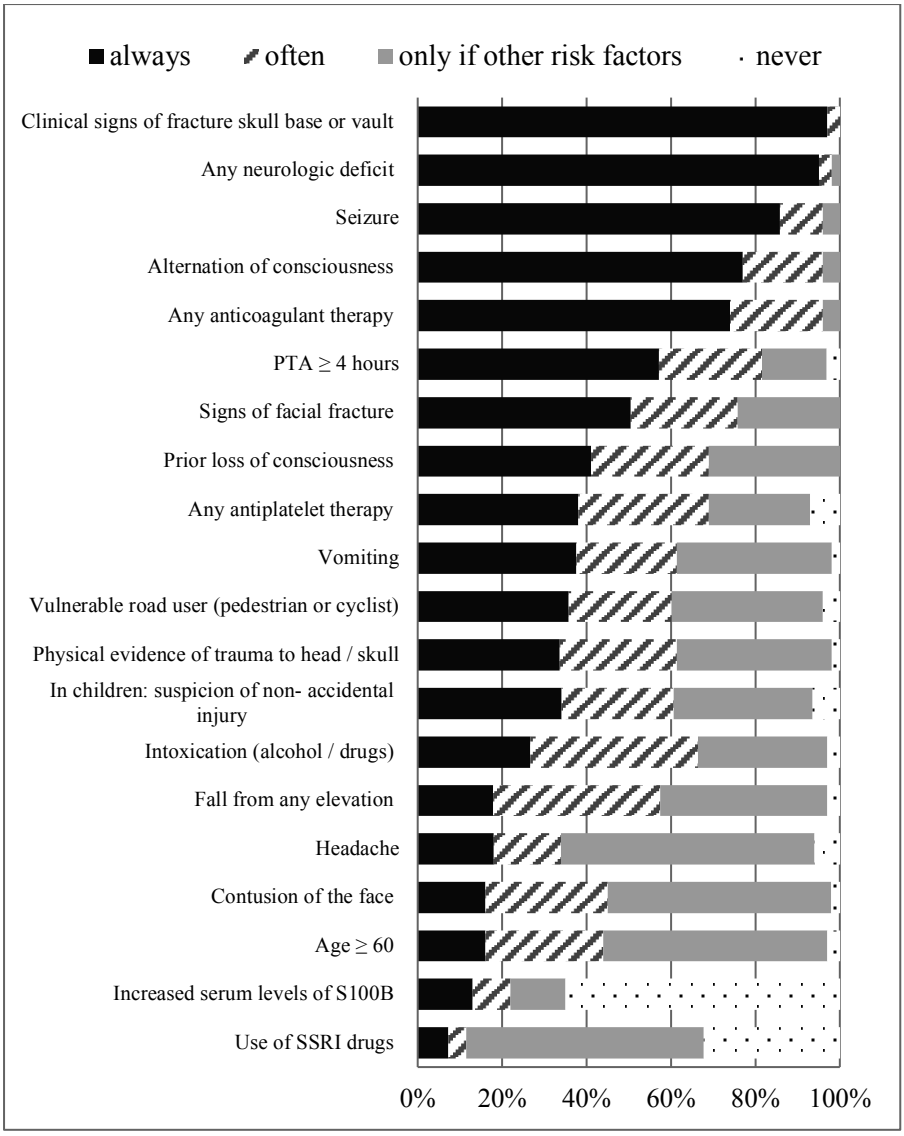


Figure 1. Frequency of ordering head CT scan in patients with mild TBI, by clinical indication
Per situation the responders had to choose the correct policy for their center: *Always/general policy:* if the situation is, in general, a reason for ward admission in your hospital. This must represent a general consensus among colleagues, rather than individual preference; *Often/partial:* the situation is often seen as a reason for ward admission in your hospital. However, it is not general practice, because not everyone in your hospital agrees or admission is only general policy in a subset of the patients; *Only in the presence of other risk factors:* if the situation is never solely a reason for ward admission, but it might be a reason in combination with one or more other risk factors; *Never*: if the situation is never the only reason for ward admission. CT= computed tomography, TBI = traumatic brain injury, PTA= post-traumatic amnesia, SSRI = selective serotonin reuptake inhibitor (medication).

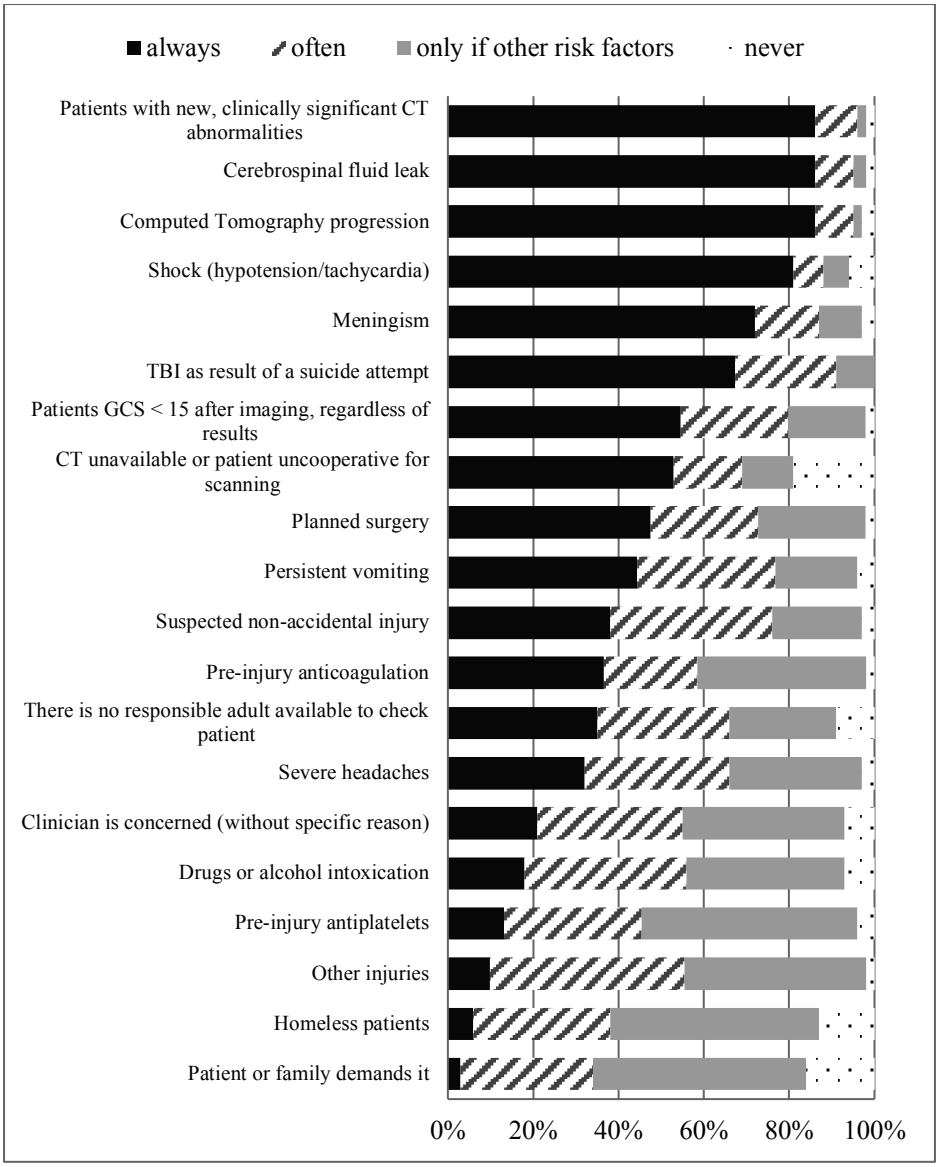


Figure 2. Frequency of ward admission of patients with mild TBI, by clinical indication
Per situation the responders had to choose the correct policy for their center: *Always/general policy:* if the situation is, in general, a reason for ward admission in your hospital. This must represent a general consensus among colleagues, rather than individual preference; *Often/partial:* the situation is often seen as a reason for ward admission in your hospital. However, it is not general practice, because not everyone in your hospital agrees or admission is only general policy in a subset of the patients; *Only in the presence of other risk factors:* if the situation is never solely a reason for ward admission, but it might be a reason in combination with one or more other risk factors; *Never*: if the situation is never the only reason for ward admission. CT = computed tomography, GCS= Glasgow Coma Scale, TBI = traumatic brain injury

When patients are admitted at the ward, GCS is assessed systematically to detect neurological deterioration. About half of the centers (n = 37; 52%) used the scheme every "half-hour for 2 hours, then hourly for 4 hours, then every 2 hours," thus in accordance with the NICE guidelines. The other half of the centers had another frequency of GCS assessment, ranging from hourly to every 24 h. In 11 centers (16%) the Galveston Orientation and Amnesia Test (GOAT), a test for post-traumatic amnesia (PTA), is systematically used at the ward and 12 centers (17%) use another form of PTA assessment.

Fifty-three centers (75%) have step-down beds for patients who no longer need intensive care unit (ICU) care but are also not well enough for a routine hospital ward. At these high-care wards, neurosurgeons (n = 32; 60%) and intensivists (n = 13; 25%) were most often in charge of the patients. Reasons for admission to the high-care wards in isolated patients with TBI included decreased consciousness level (n = 48; 68%), to monitor vital functions (n = 45; 63%), frequent GCS assessments (n = 38; 54%), confusion (n = 35; 49%), and intracranial complications (n = 32; 45%).

Treatment

Fifty-four centers (79%) state that they reverse pre-injury oral anticoagulation use if CT abnormalities are present, 46 (68%) do so if surgery was considered and 2 (3%) centers reverse anticoagulation in all patients admitted to the ward. Anticoagulation was commonly reversed with vitamin K (n = 62; 91%) or prothrombin complex concentrate (n = 55; 81%). Other treatments mentioned in this context were: fresh frozen plasma (FFP; n = 47; 69%), platelets (n = 40; 59%), fibrinogen (n = 20; 29%), and recombinant factor VII (n = 11; 16%).

If TBI patients have a CSF leak (with possibly an increased risk of infections), 34 of the centers (48%) would employ a strategy of watchful waiting before they start treatment with antibiotics. In contrast, 26 centers (37%) start antibiotics immediately and 9 (13%) start antibiotics only if patients have a fever.

TBI patients with an early seizure (a post-traumatic seizure occurring within 7 days of the trauma) receive anti-epileptic drugs (AEDs) immediately in 39 centers (55%). About one third (n = 22) start AEDs only in patients with CT abnormalities and an early seizure, and 7 centers (10%) never start AEDs in TBI patients with early seizure. Additionally, there are differences in the use of anti-seizure prophylaxis in patients with specific characteristics (Supplementary Figure 1).

Discharge information

In 38 centers (56%) guidelines are used to decide whether patients with mTBI could be discharged from the ED. In 54 centers (79%) printed discharge information is available in the ED and hospital ward to hand out to patients who are discharged home. After discharge from the ED, 42 centers (62%) provide information about

post-traumatic symptoms verbally, whereas 55 centers (78%) do so after discharge from the hospital ward. Overall, more information is provided verbally than in written form (Table 2).

Follow-up policy

A routine follow-up appointment at the outpatient clinic is scheduled in 7 centers (10%) after discharge from the ED, at a median period of 4 weeks after discharge (IQR 2.5–6). After discharge from the hospital ward, 38 centers (54%) routinely schedule a follow-up appointment at a median period of 6 weeks (IQR 4–7.8). In 16 centers (24%) patients are referred to the general practitioner, regardless of persisting symptoms. In case of persisting symptoms, the patients are advised to go back to the general practitioner (ED, n = 30, 44%; and ward, n = 17, 24%) or hospital (ED, n = 34, 50%; and ward, n = 24, 34%).

Table 2. General discharge information provided at discharge from the ED and hospital ward

	ED		Hospital ward	
Information	Verbally n (%)	Written n (%)	Verbally n (%)	Written n (%)
Details of nature and severity of injury	49 (72%)	40 (59%)	51 (72%)	47 (66%)
Symptoms that prompt patients to return for consultation	42 (62%)	58 (85%)	52 (73%)	44 (62%)
Details about the recovery process, including the fact some patients may appear to make quick recovery but later experience difficulties or complication	51 (75%)	38 (56%)	58 (82%)	30 (42%)
Contact details of community and hospital services in case of delayed complication	37 (54%)	50 (74%)	40 (56%)	45 (63%)
Information about return to everyday activities, including school/work/sports/driving	44 (65%)	37 (54%)	52 (73%)	39 (55%)
Information about post-concussion syndrome/ persisting symptoms and what to do in this situation	42 (62%)	38 (56%)	55 (78%)	22 (31%)
Information about use of pain killers and other medication	45 (66%)	45 (66%)	46 (65%)	45 (63%)
Details of support organization	39 (57%)	8 (12%)	39 (55%)	22 (31%)

ED = emergency department

Discussion

This study provides a broad overview of the current care for mTBI patients in Europe and shows that there are wide between-center variations in diagnostic, admission, and discharge policies. The most striking findings are the large variation in GCS scores that are considered a specific TBI severity, the use of CT guidelines, and policies for patients on anticoagulants. We also found large variation in follow-up policy after

discharge, where the majority of patients are not receiving routine follow-up, despite the existing evidence and guidelines for TBI.

Our findings are in line with previous research. For example, in 2001 De Kruijk and colleagues[17] performed a survey study in 67 European centers. They also reported a lack of consensus of mTBI management (e.g., definitions, guidelines) in Europe at the ED and at hospital admission. Pulhorn and associates[18] investigated management of mTBI at 19 hospital wards in Britain and also found variation in the assessment of GCS at the ward and in discharge recommendations. Our study confirms results of Stern and co-workers,[19]; they performed a survey study at the ED in 72 centers in New England and found significant variability in the use of guidelines and management of mTBI care as well.

What this study adds to previous research is that it shows that not only are guidelines not always operational in centers, but also that actual policies systematically diverge from what is recommended in those guidelines. Audits to check for adherence to the guidelines could give more insight into this, but the majority of the centers have not performed audits in the last 5 years. Moreover, our survey pinpoints areas of clinical controversy, which could do well with more clinical research.

In recent years the use of prognostic biomarkers such as s100B has been studied extensively.[20,21] The Scandinavian guidelines for mTBI even incorporated s100B in their CT scan recommendations.[22] However, in our study we observed that s100B is used as a prognostic biomarker in only 6 centers, of which 3 centers are Scandinavian.

Future research is needed to investigate whether the variation in guideline use and policies is associated with outcomes. Currently, all the participating centers are collecting patient outcomes data for the CENTER-TBI study.[13] By combining current data with data on patient outcomes, we will be able to investigate whether between-center differences in policy are associated with patient outcomes, and subsequently explore the effectiveness of different policy strategies in comparative effectiveness research (CER). CER requires variation to study effectiveness of treatments or policies by comparing centers that routinely perform an intervention with centers that do not, or that at least do so less frequently.[12] In our study we found large between-center differences that enable further study with CER approaches. For example, we can compare centers that routinely perform follow-up at the outpatient clinic, with centers that do not routinely perform follow-up and analyze the relation with outcome. And we can compare the effects of routinely giving platelets to patients on antiplatelet drugs, a procedure that has been associated with poor outcomes in spontaneous intracerebral hemorrhage (ICH), but has not been studied in TBI. Thus, in the CER context, we are actually satisfied with the observed variation in care because this provides the opportunity to compare outcomes between centers with different treatment policies.

This study has some limitations that should be taken into account when interpreting the data. The reliability of the results depends on the interpretation and willingness of the investigators to be truthful and transparent in their answers. We tried to enhance this by explicitly asking for general policy rather than individual preferences and explained all answer options carefully. Further, because the majority of participating centers were academic level 1 trauma centers, the findings might not be generalizable to centers with a lower trauma center designation. However, we believe the variation in policies will only increase when also lower trauma center designations are included.

Conclusion

Large between-center variations exist in policies for diagnostics, admission, and discharge decisions in patients with TBI at the ED and at the hospital ward. The results of this study may be useful in the understanding of TBI care in Europe and show the need for further studies on the effect of different policies on patient outcomes.

References

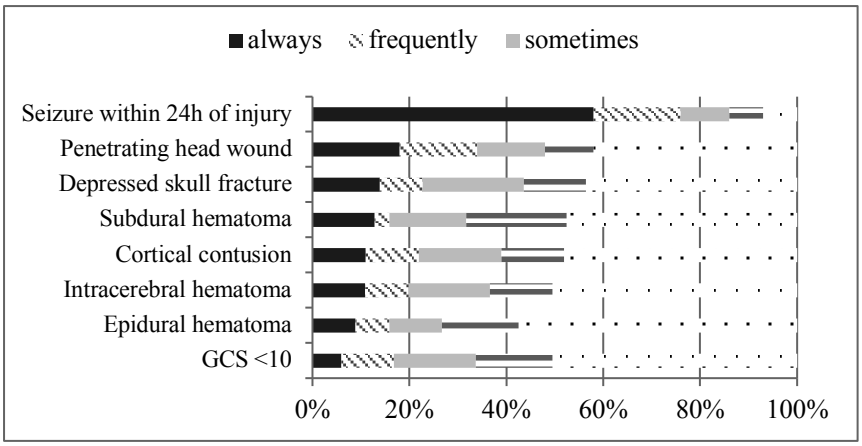
1. Tagliaferri F, Compagnone C, Korsic M, et al. A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien) 2006;148(3):255-68; discussion 68.
2. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 2015;157(10):1683-96.
3. Teasdale G, Maas A, Lecky F, et al. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol 2014;13(8):844-54.
4. Esselman PC, Uomoto JM. Classification of the spectrum of mild traumatic brain injury. Brain Inj 1995;9(4):417-24.
5. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet 2001;357(9266):1391-6.
6. National Clinical Guideline C. National Clinical Guidance Centre. (2014). CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults. . National Institute for Health and Care Excellence 2014.
7. Smits M, Dippel DW, Steyerberg EW, et al. Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med 2007;146(6):397-405.
8. Borg J, Holm L, Cassidy JD, et al. Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004(43 Suppl):61-75.
9. Carroll LJ, Cassidy JD, Peloso PM, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004(43 Suppl):84-105.
10. Borg J, Holm L, Peloso PM, et al. Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004(43 Suppl):76-83.
11. Vos PE, Battistin L, Birbamer G, et al. EFNS guideline on mild traumatic brain injury: report of an EFNS task force. Eur J Neurol 2002;9(3):207-19.
12. 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 2012;29(1):32-46.
13. 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.
14. 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.
15. Unden, J., Ingebrigsten, T., Romner, B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: An evidence and consensus-based update. BMC Med. 2013; 11, 50
16. Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. N Engl J Med 2000;343(2):100-5.
17. De Kruijk JR, Twijnstra A, Meerhoff S, et al. Management of mild traumatic brain injury: lack of consensus in Europe. Brain Inj 2001;15(2):117-23.
18. Pulhorn H, Westmoreland L, McMahon C. The management of minor head trauma (GCS 15-13) across a Trauma Network. Br J Neurosurg 2016;30(5):536-40.
19. Stern RA, Seichepine D, Tschoe C, et al. Concussion Care Practices and Utilization of Evidence-Based Guidelines in the Evaluation and Management of Concussion: A Survey of New England Emergency Departments. J Neurotrauma 2016.

20. Hergenroeder GW, Redell JB, Moore AN, et al. Biomarkers in the clinical diagnosis and management of traumatic brain injury. Mol Diagn Ther 2008;12(6):345-58.
21. Topolovec-Vranic J, Pollmann-Mudryj MA, Ouchterlony D, et al. The value of serum biomarkers in prediction models of outcome after mild traumatic brain injury. J Trauma 2011;71(5 Suppl 1):S478-86.
22. Unden L, Calcagnile O, Unden J, et al. Validation of the Scandinavian guidelines for initial management of minimal, mild and moderate traumatic brain injury in adults. BMC Med 2015;13:292.

Supplementary Table 1. Implementation of CT guidelines at ED by no of centers

	N (%)
Implementing	
No formal implementation of guidelines	12 (18%)
Verbal direction from clinical managers/ clinical directors/senior doctors	22 (32%)
Written protocols and algorithms	38 (56%)
Training organized by your own hospital / department	15 (22%)
E-learning	3 (4%)
Flowchart/algorithms/protocols in the patient data management system of ED	10 (15%)
Periodic feedback on adherence to the guideline	6 (9%)
Structural attention for protocol adherence during clinical rounds	5 (7%)
Other	2 (3%)
Who oversees guideline development and maintenance at ED	
Individual	5 (7%)
Group: ED physicians	7 (10%)
Group: neurosurgeons	3 (4%)
Group: trauma surgeons	1 (2%)
Group: neurologist	2 (3%)
Group: multidisciplinary	33 (49%)
Neither	13 (19%)
Time period of audits* to check for adherence to guidelines at ED	
Not in the last five years	27 (40%)
Once in the last five years	9 (14%)
Approximately 2-4 times in the last five years	11 (16%)
On a yearly basis	9 (13%)
Several times a year	5 (7%)
Adherence to the CT guidelines at ED considered	
0-25% of cases	3 (4%)
25-50% of cases	4 (6%)
50-75% of cases	21 (31%)
75-100% of cases	28 (41%)
N/A	11 (16%)

*An audit is a process by which your hospital / ED assesses how well guidelines are followed.



Supplementary Figure 1. Frequency of anti-epileptic drug prescription, by indication. Per situation the responders had to choose the correct policy for their center: *Always/general policy:* if the situation is, in general, a reason for ward admission in your hospital. This must represent a general consensus among colleagues, rather than individual preference; *Often/partial:* the situation is often seen as a reason for ward admission in your hospital. However, it is not general practice, because not everyone in your hospital agrees or admission is only general policy in a subset of the patients; *Only in the presence of other risk factors:* if the situation is never solely a reason for ward admission, but it might be a reason in combination with one or more other risk factors; *Never*: if the situation is never the only reason for ward admission. GCS= Glasgow Coma Scale

Chapter 3

Practice variation in admission and discharge management of mild traumatic brain injury patients at the emergency department in Europe: a CENTER-TBI study.

In preparation

Kelly A. Foks
Hester F. Lingsma
Diederik W.J. Dippel
Andrew I.R. Maas
David Menon
Fiona E. Lecky
Ewout W. Steyerberg
Suzanne Polinder
CENTER-TBI investigators and participants

Chapter 4

Impact of guidelines for minor head injury on the utilization and diagnostic yield of CT over two decades, using natural language processing in a large dataset

European Radiology 2019

Kelly A. Foks
Ewoud Pons
Diederik W.J. Dippel
Myriam G.M. Hunink

Abstract

Objective: We investigated the impact of clinical guidelines for the management of minor head injury on utilization and diagnostic yield of head CT over two decades.

Methods: Retrospective before-after study using multiple electronic health record data sources. Natural language processing algorithms were developed to rapidly extract indication, Glasgow Coma Scale, and CT outcome from clinical records, creating two datasets: one based on all head injury CTs from 1997 to 2009 ($n = 9109$), for which diagnostic yield of intracranial traumatic findings was calculated. The second dataset (2009–2014) used both CT reports and clinical notes from the emergency department, enabling selection of minor head injury patients ($n = 4554$) and calculation of both CT utilization and diagnostic yield. Additionally, we tested for significant changes in utilization and yield after guideline implementation in 2011, using chi-square statistics and logistic regression.

Results: The yield was initially nearly 60%, but in a decreasing trend dropped below 20% when CT became routinely used for head trauma. Between 2009 and 2014, of 4554 minor head injury patients overall, 85.4% underwent head CT. After guideline implementation in 2011, CT utilization significantly increased from 81.6 to 87.6% ($p = 7 \times 10^{-7}$), while yield significantly decreased from 12.2 to 9.6% ($p = 0.029$).

Conclusions: The number of CTs performed for head trauma gradually increased over two decades, while the yield decreased. In 2011, despite implementation of a guideline aiming to improve selective use of CT in minor head injury, utilization significantly increased.

Introduction

Non-contrast head CT is routinely used to rule out intracranial complications after (blunt) head trauma, but for patients with minor head injury (MHI) or mild traumatic brain injury—Glasgow Coma Scale (GCS) ≥ 13—CT is not always necessary.[1,2] Intracranial traumatic findings are seen on 7–12% of CTs, although less than 1% of MHI patients require surgery, due to severe complications such as intracranial hematomas.[3-6] Over time, several guidelines have been developed to assess the risk of intracranial complications, using patient characteristics at presentation, such as vomiting or amnesia.[3-5,7] These guidelines enable selective use of CT, with the goal to avoid unnecessary imaging and therefore reduce utilization. When comparing commonly used guidelines for MHI, the inherent trade-off between sensitivity and specificity with varying cutoff criteria is seen, leading to variation in the number of unnecessary head CTs and missed intracranial findings.[8]

The purpose of implementing guidelines is to promote appropriate utilization which leads to safe, cost-effective practice that provides high-quality patient care. In the context of MHI, guidelines commonly reduce utilization. Nevertheless, several studies reported increased utilization of CT after guidelines for selective use were implemented, leading to higher costs, longer waiting times, and additional radiation risk.[9-13] After implementation of validated imaging guidelines, it is important to assess their effectiveness in routine clinical practice. Both utilization (i.e., the proportion of patients that undergo imaging) and diagnostic yield (i.e., the proportion of imaging procedures with relevant findings) are important indicators for appropriate use of imaging.

The study purpose is to assess the impact of imaging guidelines for the management of MHI in routine clinical practice, by measuring both utilization and diagnostic yield of CT over two decades. We hypothesized that implementation of improved guidelines for selective use of CT would result in decreased utilization and consequentially also increased diagnostic yield over time.

The large number of clinical records related to MHI in this timeframe made manual review unfeasible. Natural language processing (NLP) can be used to extract structured variables from electronic free text and has been successfully applied to various sources in the electronic health record (EHR), including radiology reports.[14,15] Therefore, NLP methods were developed to facilitate large dataset analytics of two decades of EHR sources.

Methods

We performed a retrospective before-after study using multiple EHR data sources from an urban, academic, level 1 trauma center for MHI patients presenting at the emergency department (ED). Part of the data was prospectively collected in the CT in Head Injury Patients (CHIP) study.[4]

Sources and data collection

Several data sources related to MHI were obtained from the EHR, containing information on presentation, diagnostic imaging results, and other potentially relevant clinical outcomes: these sources included clinical notes from neurology, non-contrast head CT reports, neurosurgery registrations, hospitalization records, and various metadata (i.e., age, gender, and time of death for deceased patients).

NLP development and performance assessment

Four NLP algorithms were developed to: 1. Select acute head trauma cases from clinical notes; 2. Extract GCS score from clinical notes; 3. Select reports ordered for traumatic indication from all head CTs; and 4. Select head CT reports describing any intracranial traumatic finding.

Each NLP algorithm was trained on a set of reference documents, for which two or more clinicians manually labeled all information that should be extracted by NLP. The NLP algorithms for selecting acute head traumas and extracting GCS score were both trained using 500 labeled clinical notes from presentation. Additionally, traumatic indication was manually labeled in 500 head CTs, which were used for training the third NLP algorithm, in order to select traumatic cases from radiology reports directly—before clinical notes were documented electronically in time. Finally, 1934 CT head reports from 2002 to 2003 that had been labeled by our institute during the CHIP study were used to train the fourth NLP algorithm.[4] Therefore, this algorithm selects CT reports with any intracranial traumatic finding (i.e., depressed fracture, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, (non)hemorrhagic contusion, diffuse axonal injury, and intraventricular hemorrhage).

The first NLP algorithm for selecting acute head injuries was optimized for sensitivity to ensure completeness of the data. The fourth algorithm was optimized to balance false positives and false-negative detection of intracranial traumatic findings in a one-to-one ratio, to prevent potential changes in prevalence. During NLP development, 10-fold cross-validation was performed on the labeled reference sets, calculating sensitivity and specificity to measure the performance of all four NLP algorithms.

Dataset creation and validation

After performance evaluation, the four NLP algorithms were applied to all available clinical records (of the type used for training) to extract structured information. Radiology reports were available in digital format from 1997, while clinical notes only existed in the EHR from 2008. Therefore, the extracted variables were grouped into two distinct datasets (Figure 1).

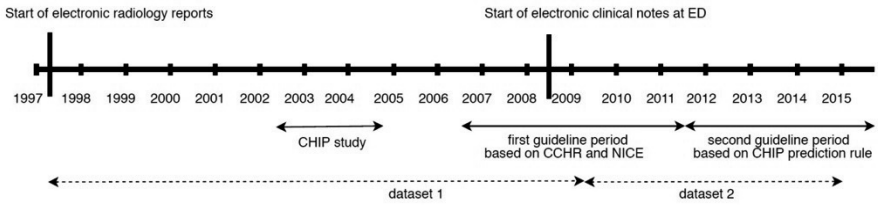


Figure 1. Timeline of guidelines used in the study center and the generated datasets.
Dataset 1 contains data extracted from electronic radiology reports between 1997 and 2009 for patients with minor, moderate, and severe head injury; dataset 2 contains data extracted from electronic radiology reports and electronic clinical notes between 2009 and 2014, only for patients with minor head injury. CHIP = CT in head injury patients; CCHR = Canadian CT Head Rule; NICE = National Institute for Health and Care Excellence

The first dataset was created by using the NLP algorithms three and four on all radiology reports from 1997 to 2009. This dataset contains minor, moderate, and severe head injury patients, containing CT reports as well as conventional X-ray of the head, which historically had been the first diagnostic test in the workup of head trauma.

The second dataset was created from both CT and clinical reports from 2009 to 2014, using NLP algorithms one, two, and four. Patients with GCS score < 13 were discarded, purposely resulting in a MHI dataset. This dataset also contained all clinical outcomes occurring within 30 days of presentation: hospitalization, neurosurgical intervention, and death. These outcomes were manually checked to ensure no critical lesions were missed by the initial head CT. Furthermore, integrity of this dataset was assessed by inspecting 100 randomly selected entries for completeness and correctness.

Guideline implementation over time

During the study timeframe, different diagnostic guidelines for MHI were used (Figure 1). Until 2002, CT was mainly performed in MHI patients after detection of skull fractures on X-ray. From 2002 to 2004, the study center conducted the prospective CHIP study to investigate the risk factors of MHI, during which patients with GCS score of 13–14 and all patients with GCS score of 15 and at least one risk factor underwent CT (Supplementary Table 1).

In 2006, the first local MHI guideline was implemented. This guideline was based on the Canadian CT Head Rule (CCHR) and the National Institute for Clinical Excellence (NICE) guideline to safely reduce CT utilization; CT was indicated in patients with GCS 15 and one risk factor, or a combination of specific risk factors (Supplementary Table 1).[3,5]

In 2011, the second MHI guideline was implemented based on the CHIP rule.[4] This guideline was developed to achieve a higher reduction in CTs, while identifying all patients with serious complications that require surgery; CT was indicated for patients with one major criterion or two minor criteria (Supplementary Table 1).

The guideline implementation process remained stable over the years; at the study center, guidelines were based on national guidelines and developed in multidisciplinary groups, and regular updates were performed. The guidelines were presented to the involved clinical departments, formally approved by department staff and could easily be consulted online.

Statistical analysis

We calculated the diagnostic yield for both datasets by taking the proportion of positive findings from all CTs performed after trauma. Additionally, in the second dataset, we calculated utilization as the proportion of all MHI patients who underwent CT. The second dataset was split into two periods: period one, before implementation of the new CHIP-based guideline (June 2009–September 2011) and period two, after implementation (June 2012–September 2014). The datasets contained the same months to prevent bias due to seasonal variation. Furthermore, the datasets were separated by nine months to ensure the second guideline was fully operational at the start of the period. Descriptive statistics for patient demographics and outcomes were generated. We calculated the chi-squared statistic to compare both the utilization and yield of CT between the two periods. We performed logistic regression for the effect of time on both utilization and yield during each period independently, to test whether any significant trend existed within the periods. Finally, we compared the outcomes with the results of the CHIP study in the study center. Statistical analysis was performed with R software, version 3.3.2.

Results

Sources and data collection

We obtained 17,237 clinical notes documented by neurology in the ED, 27,759 non-contrast head CT reports, 2088 conventional skull X-ray reports, 10,207

neurosurgical procedure registrations, 4497 hospitalizations, and 2404 records of patients who had died (i.e. irrespective of the cause of death).

NLP performance assessment

NLP performance on 500 manually labeled clinical notes showed a 93.7% sensitivity and 97.4% specificity for the selection of acute head trauma cases, and a 97.5% sensitivity and 100% specificity for extraction of GCS score. Traumatic indication was determined with 95.8% sensitivity and 95.5% specificity on 500 manually labeled head CTs. Intracranial traumatic findings were identified with 86.8% sensitivity and 98.8% specificity on 1943 labeled head CT reports from the CHIP study. NLP errors during performance evaluation increased the tested prevalence by merely 0.25% compared to the training data.

Dataset creation and validation

The first dataset, based only on 18,606 radiology reports from 1997 to 2009, consisted of 9109 patients with a head CT for a traumatic indication. The second dataset, based on 9153 radiology reports and 17,237 clinical reports from 2009 to 2014, consisted of 4554 MHI patients.

After inspection of 100 patients in the second dataset, we found eight patients in which the NLP algorithms identified incorrect information from the clinical records. Three were incomplete due to extraction errors (a positive scan was missed once, while an incorrect GCS was selected twice). In one patient, imaging was scheduled according to the clinical notes, but the CT report was unavailable. NLP failed to exclude two trauma patients without apparent head injury and included one patient with a previous trauma in the history. One patient was incorrectly selected after transfer from another hospital. These results are consistent with the NLP performance evaluation. Inspection of the follow-up outcomes within 30 days did not identify any misdiagnosed intracranial traumatic findings.

Dataset 1: Historical perspective of diagnostic yield for trauma of any severity (1997–2009)

Of 9109 patients who underwent a CT after sustaining a head injury, 18.0% ($n = 1641$) had intracranial traumatic findings on CT. Over time, more CTs were performed whereas the amount of skull X-rays diminished (Figure 2A). During the early years, a low number of CTs were performed, most of which were positive resulting in a very high diagnostic yield. From 1997, the yield was initially nearly 60%, but a decreasing trend consolidated below 20% around 2002 (Figure 2B), which illustrates that CT had become routinely used for head trauma. The effect of the CHIP study is somewhat noticeable in the lower yield associated with scanning all patients.

In subsequent years, more CTs were performed with a relatively constant number of positive findings, resulting in a lower yield (Figure 2A,B).

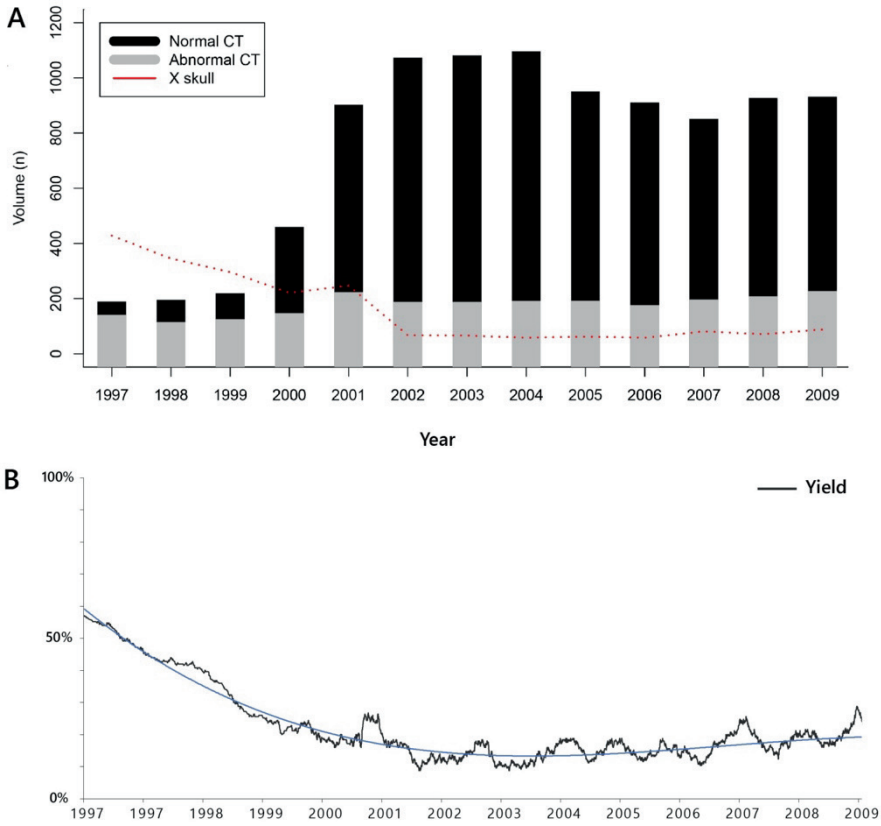


Figure 2. Historical perspective of CT use in patients with minor, moderate, and severe head injury from 1997 to 2009.
A. Number of patients with minor, moderate, and severe head injury and CT. The red line corresponds to skull X-ray performed for both traumatic and non-traumatic indications.
B. Yield of CT in minor, moderate, and severe head injury patients. To calculate yield for an exact point in time, we used a smoothed average of 125 entries before and after that date to calculate the proportion of positive findings.

Dataset 2: Utilization and diagnostic yield of CT in MHI patients (2009–2014)
For 4554 patients with MHI seen at the ED, the mean age of 45.1 (SD ± 20.3) years and most patients had GCS 15 ($n = 3219$; 70.7%) at presentation (Table 1). CT was performed in 3887 patients (85.4%), identifying 414 (9.1%) intracranial traumatic findings. Over time, the utilization of CTs in MHI increased, and the absolute number

of positive findings on CT was stable, resulting in a decreasing diagnostic yield (Figure 3A). Nine hundred seventy-seven patients (20%) were admitted to the hospital wards, and eight patients (0.18%) had a neurosurgical intervention within 30 days after injury. None of the patients without a head CT had a neurosurgical intervention within 30 days after the injury.

Table 1. Characteristics of patients before and after implementation of a new minor head injury guideline

	CHIP study[e] (n=2193)	First period (n=1429)	Second period (n=2265)	Entire cohort (n=4554)
Period	Feb 2002 – Aug 2004	June 2009 - Sept 2011	June 2012 - Sept 2014	June 2009 – Sept 2014
Men	1575 (71.8%)	1051 (73.5%)	1536 (67.8%)	3196 (70.2%)
Mean age in years (SD)	40.3(±18.1)	43.4 (±20.1)	46.5 (±20.5)	45.1 (±20.3)
Emergency department				
GCS 13	106 (4.8%)	109 (7.6%)	116 (5.1%)	291 (6.4%)
GCS 14	387 (17.6%)	414 (29.0%)	440 (19.4%)	1044 (22.9%)
GCS 15	1661 (75.7%)	906 (63.4%)	1709 (75.5%)	3219 (70.7%)
Use of CT[a]	2193 (100%)	1166 (81.6%)	1984 (87.6%)	3887 (85.4%)
Any intracranial traumatic finding on CT (prevalence)	155 (7.1%)	142 (9.9%)	191 (8.4%)	414 (9.1%)
Yield of CT[b]	7.1%	12.2%	9.6%	10.7%
Follow-up				
Admission to hospital[c]	-	713 (49.9%)	990 (43.7%)	2067 (45.4%)
Neurosurgical intervention (<30 days after injury)	11 (0.50%)	3 (0.21%)	3 (0.13%)	8 (0.18%)
Death (<30 days after presentation)[d]	-	8 (0.56%)	21 (0.93%)	33 (0.72%)

[a]Proportion of CT use in minor head injury patients. [b]Fraction positive findings. [c]Reason for admission to hospital unknown. [d]Unknown cause of death. [e]Patients with minor and at least one risk factor were included in this study. *CHIP*, CT in head injury patients; *GCS*, Glasgow Coma Scale; *ED*, emergency department; *CT*, computed tomography

Impact of CT guidelines (second dataset)

During the CHIP study from 2002 to 2004, 2193 patients received a CT and 155 (7.1%) had intracranial traumatic findings (4). Eleven patients (0.50%) received a neurosurgical intervention within 30 days after injury.

The first guideline was used in 1429 patients from 2009 to 2011 (Table 1). Most patients were referred by ambulance ($n = 944$; 66.1%); only 26 patients were referred by a general practitioner (1.8%) and 370 patients (25.9%) came to the ED at their own initiative. In 1166 patients (81.6%), a head CT was performed 142 (9.9%) had intracranial traumatic findings. The overall yield for the first period was 12.2%. Seven hundred thirteen patients (49.9%) were hospitalized and three of 1429 patients (0.21%) underwent a neurosurgical intervention within 30 days after injury.

The second guideline was used in 2265 patients from 2012 to 2014. One thousand five hundred two patients (66.3%) were referred by ambulance, 38 (1.7%) by a general practitioner, and 614 (27.1%) came at their own initiative. In 1984 patients (87.6%) a CT was performed, 191 patients (8.4%) had intracranial traumatic findings. The overall yield for the second period was 9.6%. Nine hundred ninety patients (43.7%) were hospitalized, and three patients (0.13%) underwent a neurosurgical intervention within 30 days after injury.

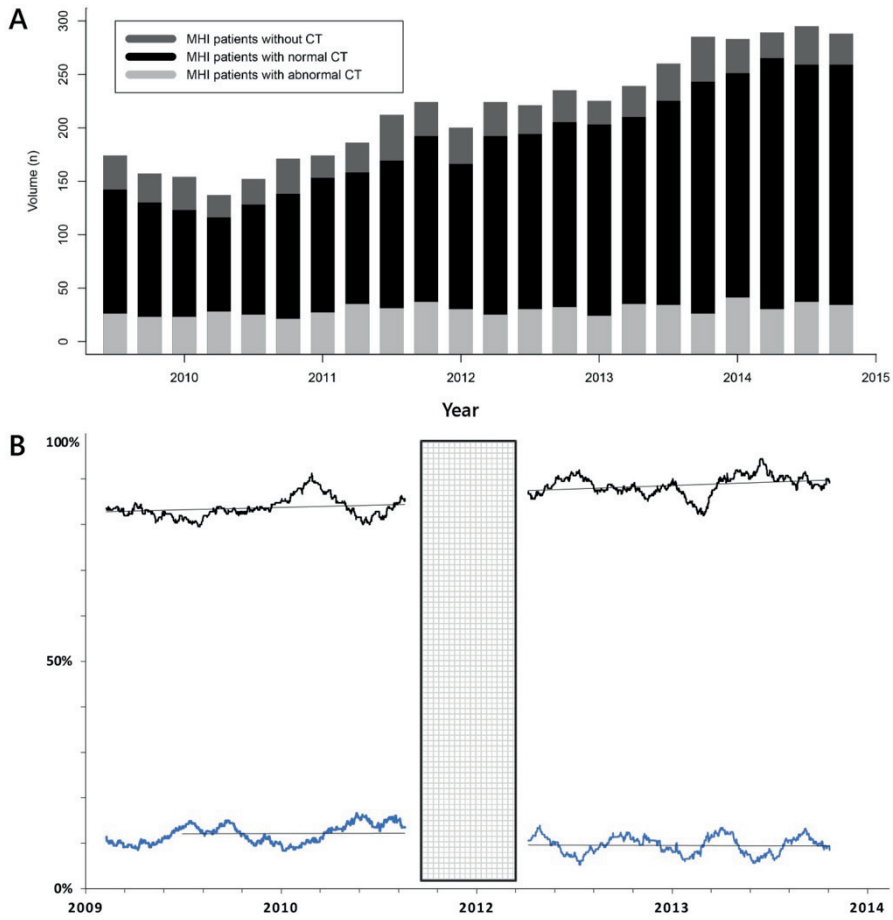


Figure 3. Use and yield of CT in minor head injury patients from 2009 to 2014, before and after implementation of the second guideline.
A. Number of patients with minor head injury and CT.
B. Use (black) and yield (blue) of CT in minor head injury patients; the gray area denotes the timeframe for implementation of the second guideline. To calculate yield for an exact point in time, we used a smoothed average of 125 entries before and after that date to calculate the proportion of positive findings

The overall increase in utilization and decrease in diagnostic yield between the two guideline periods were both statistically significant (utilization $p = 7 \times 10^{-7}$ and yield $p = 0.029$). Within the periods individually, we found a slightly increasing trend of yield, and during the second period, a slightly decreasing trend of yield (Figure 3B). Both slopes were not statistically significant compared to zero (Table 2).

Table 2. The effect of time on use and yield of CT (2009–2014)

	First period (June 2009 - September 2011)			Second period (June 2012 – September 2014)		
	Overall %	β	p	Overall %	β	p
Use	81.6	1.09×10^{-4}	0.693	87.6	1.91×10^{-4}	0.473
Yield	12.2	2.96×10^{-4}	0.330	9.6	1.87×10^{-4}	0.649

Estimated with logistic regression, where β is the increase in log odds ratio per day

Discussion

This study investigated the impact of clinical guidelines for the management of MHI in routine clinical practice, by assessing both utilization of CT and diagnostic yield for intracranial findings in all available electronic patient records from two decades, facilitated by NLP. After implementation of a CHIP-based guideline in 2011, the utilization of CT increased significantly, while the yield significantly decreased. Within the periods before and after the guideline change, no significant trend was found for both utilization and yield, indicating that the before-after difference can be attributed to the guideline change and is not due to a preexisting trend. Therefore, implementation of improved guidelines for selective use of CT did not reduce utilization as we expected.

Our center conducted the CHIP study from 2002 to 2004, during which all MHI patients and at least one risk factor underwent CT.[4] When all the patients were scanned, the yield is approximately equal to the prevalence. This enabled us to compare the prevalence from the CHIP study period with the yield resulting from guideline use in routine clinical practice. The yield of CT during the CHIP study was 7.1%, whereas between 2009 and 2014, selective use of CT caused a higher yield of 10.7%. The overall prevalence of intracranial traumatic findings during both guideline periods was higher (9.1%) compared to the CHIP study (7.1%). The case mix during the CHIP study may have been slightly different from patients seen by neurology at the ED in routine clinical care. Importantly, this difference is not applicable to the guideline comparison, and both percentages are in line with the known incidence of intracranial traumatic findings.[3-5]

The first guideline employed in our center reduced CT utilization by 18.4% compared to scanning all patients. In 2011, the CHIP-based guideline was implemented, and the potential CT reduction compared to scanning all patients was estimated at 23–30%, but we only showed a CT reduction of 12.4%. This lower reduction might be explained by more lenient use of the CHIP criteria in routine

clinical practice. While during the first guideline period, the scanning policy was effectively stricter with significantly better CT reduction; not all patients with intracranial traumatic findings were identified.[8,16,17] Although the risk of serious traumatic findings requiring surgery is very low, scanning all MHI patients is more cost-effective than missing only a small portion of serious traumatic findings due to selective scanning.[18,19] Thus, if the CHIP rule facilitates detection of all serious traumatic findings, while reducing CT use by 12%, this would be preferred to scanning all patients. We have shown the effect of using a CHIP-based guideline for selective scanning in routine clinical practice, and similar results were shown in a recent external validation study with a substantial reduction in CTs in clinical practice.[20] In the hypothetical situation that CT guidelines had not been implemented, in all likelihood, all patients with at least one risk factor would be scanned similar to the CHIP study period. This would almost completely eliminate any potential CT reduction.

To evaluate the purported impact of guidelines, information about guideline adherence by clinical physicians is necessary. However, for our study period, this information was not available. Furthermore, guideline adherence may affect CT utilization; however, we have no reason to assume that implemented guidelines were treated differently in one of the periods. Previous small studies about adherence of different CT guidelines showed an adherence in 51–100% of the patients.[21-24] Guideline adherence in our center cannot be expected to be 100% for the study data, which might have led to a lower CT reduction than expected. Additionally, introduction of a new guideline may also have resulted in enhanced awareness among clinicians for the risk factors in MHI, which may have caused increased utilization of CT.[25] The purpose of guideline implementation is to optimize clinical practice and care. Therefore, guideline implementation does not necessarily lead to a decrease in imaging utilization—in fact, it may lead to an increase in imaging if previously underutilized.

Besides guideline use, other factors such as increased presentation and different referral patterns by a general practitioner or ambulance can influence CT use. We found that during the second period, the number of patients seen in the ED had increased substantially (from 2265 to 1429). This increase cannot be explained by a difference in case mix because both demographic characteristics, as well as referral patterns by general practitioners and ambulance personnel remained the same. However, the increase is in line with previous research based on national registries which identified more head injury patients presenting to the ED.[11] It is unclear whether this is caused by a potential increase in risky behavior, a higher tendency to seek urgent medical care. Other potential reasons may be an improvement of existing imaging technology, fear of litigation, or change of institutional culture, for example attitudes towards risk of missing diagnoses. Because of the increasing number of

patients and the increase in the use of imaging, efficient use of CT scanning is now more required than ever.[8,26,27]

Despite, or maybe because of, scanning more patients in the second period, the number of patients admitted to the hospital was lower (49.9% vs 43.7%), which may be favorable to healthcare costs.[28] Increased CT use can lead to increased confidence among physicians that no serious injury is present and thus allows discharge from the ED without admission to the hospital. Increased use may reflect cost-conscious changes in management.

The strength of NLP enabled the extraction of large numbers of clinical variables from heterogenous EHR sources. In prior studies, NLP was used to assess diagnostic yield by extracting the imaging outcome from radiology reports.[29,30] To our knowledge, this is the first study that investigated both the utilization and yield of diagnostic imaging by automatically extracting the indication as well as imaging outcome from free text, using multiple NLP algorithms on heterogenous EHR sources. Automatic information extraction enables the review of large numbers of textual documents but, equivalent to manual chart review, is not faultless. However, this has been shown to have limited impact, because extraction of traumatic cases and GCS was successfully optimized for very high specificity, resulting in mostly true cases in the final database. Also, during the performance evaluation, the prevalence of intracranial findings increased only by 0.25% due to errors. Any remaining errors can be assumed to affect all periods equally.

To conclude, in this large study using NLP, we showed that the number of head CTs performed for head injury gradually increased over two decades, while the diagnostic yield for intracranial traumatic findings demonstrated a decreasing trend. In 2011, despite implementation of an updated guideline aiming to improve selective use of CT for MHI, utilization significantly increased, while diagnostic yield significantly decreased. NLP is a valuable tool to monitor utilization and diagnostic yield of imaging as a potential quality-of-care indicator.

References

1. Vos PE, Battistin L, Birbamer G, et al. EFNS guideline on mild traumatic brain injury: report of an EFNS task force. Eur J Neurol. 2002;9(3):207-19.
2. Borg J, Holm L, Cassidy JD, et al. Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):61-75.
3. Haydel MJ, Preston CA, Mills TJ, Luber S, Blaudeau E, DeBlieux PM. Indications for computed tomography in patients with minor head injury. N Engl J Med. 2000;343(2):100-5.
4. Smits M, Dippel DW, Steyerberg EW, et al. Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med. 2007;146(6):397-405.
5. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet. 2001;357(9266):1391-6.
6. af Geijerstam JL, Britton M. Mild head injury - mortality and complication rate: meta-analysis of findings in a systematic literature review. Acta Neurochir (Wien). 2003;145(10):843-50;
7. Pandor A, Goodacre S, Harnan S, et al. Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technol Assess. 2011;15(27):1-202.
8. Smits M, Dippel DW, de Haan GG, et al. Minor head injury: guidelines for the use of CT--a multicenter validation study. Radiology. 2007;245(3):831-8.
9. van den Brand CL, Rambach AH, Postma R, et al. Practice guideline 'Management of patients with mild traumatic head/brain injury' in the Netherlands. Ned Tijdschr Geneeskd. 2014;158:A6973. PMID: 24518845
10. Shravat BP, Huseyin TS, Hynes KA. NICE guideline for the management of head injury: an audit demonstrating its impact on a district general hospital, with a cost analysis for England and Wales. Emerg Med J. 2006;23(2):109-13.
11. Van den Brand CL, Karger LB, Nijman ST, Hunink MG, Patka P, Jellema K. Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. Eur J Emerg Med. 2017.
12. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 2017;16(12):987-1048.
13. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med. 2007;357(22):2277-84.
14. Kreimeyer K, Foster M, Pandey A, et al. Natural language processing systems for capturing and standardizing unstructured clinical information: A systematic review. J Biomed Inform. 2017;73:14-29.
15. Pons E, Braun LM, Hunink MG, Kors JA. Natural Language Processing in Radiology: A Systematic Review. Radiology. 2016;279(2):329-43.
16. Smits M, Dippel DW, de Haan GG, et al. External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. Jama. 2005;294(12):1519-25.
17. Bouida W, Marghli S, Souissi S, et al. Prediction value of the Canadian CT head rule and the New Orleans criteria for positive head CT scan and acute neurosurgical procedures in minor head trauma: a multicenter external validation study. Ann Emerg Med. 2013;61(5):521-7.
18. Holmes MW, Goodacre S, Stevenson MD, Pandor A, Pickering A. The cost-effectiveness of diagnostic management strategies for adults with minor head injury. Injury. 2012;43(9):1423-31.
19. Smits M, Dippel DW, Nederkoorn PJ, et al. Minor head injury: CT-based strategies for management--a cost-effectiveness analysis. Radiology. 2010;254(2):532-40.

20. Foks KA, van den Brand CL, Lingsma HF, et al. External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands. Bmj 2018;362:k3527
21. National Clinical Guidance Centre. CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults . National Institute for Health and Care Excellence. 2014. PubMed PMID: 25340248.
22. Haydon NB. Head injury: audit of a clinical guideline to justify head CT. J Med Imaging Radiat Oncol. 2013;57(2):161-8.
23. Mooney JS, Yates A, Sellar L, et al. Emergency head injury imaging: implementing NICE 2007 in a tertiary neurosciences centre and a busy district general hospital. Emerg Med J. 2011;28(9):778-82.
24. Heskestad B, Baardsen R, Helseth E, Ingebrigtsen T. Guideline compliance in management of minimal, mild, and moderate head injury: high frequency of noncompliance among individual physicians despite strong guideline support from clinical leaders. J Trauma. 2008;65(6):1309-13.
25. Rohacek M, Albrecht M, Kleim B, Zimmermann H, Exadaktylos A. Reasons for ordering computed tomography scans of the head in patients with minor brain injury. Injury. 2012;43(9):1415-8.
26. Bellolio MF, Heien HC, Sanglaralingham LR, et al. Increased computed tomography utilization in the emergency department and its association with hospital admission. West J Emerg Med. 2017;18(5):835-845.
27. Brinkjikji W, Kallmess DF, Cloft HJ. Rising utilization of CT in adult fall patients. AJR. 2015;204(3):558-62.
28. Af Geijerstam JL, Britton M, Marke LA. Mild head injury: observation or computed tomography? Economic aspects by literature review and decision analysis. Emerg Med J. 2004;21(1):54-8.
29. Dreyer KJ, Kalra MK, Maher MM, et al. Application of recently developed computer algorithm for automatic classification of unstructured radiology reports: validation study. Radiology. 2005;234(2):323-9.
30. Raja AS, Ip IK, Prevedello LM, et al. Effect of computerized clinical decision support on the use and yield of CT pulmonary angiography in the emergency department. Radiology. 2012;262(2):468-74.

Supplementary Table 1. Criteria indicating the need for a CT over time

CHIP study	First local guideline	Second local guideline
2002-2004	2006-2011	2011- present time
GCS 13-14: always CT GCS 15 and at least 1 risk factor: - LOC - Short term memory loss - Amnesia for traumatic event - Posttraumatic seizure - Vomiting - Serious headache - Clinical suspicion of intoxication with drugs or alcohol - Injury above clavicle - Neurologic deficit*	GCS ≤14: always CT GCS 15 and at least 1 risk factor: - Focal neurologic deficit [a] - Clinical signs of skull base fracture [b] - Vomiting more than once - Retrograde amnesia > 30 minutes LOC or PTA and: - Age ≥ 65 year - Use of anticoagulants, coagulopathy or chronic alcohol abuse - Dangerous trauma mechanism [c] - Posttraumatic seizure	Major criteria (1 or more perform CT) - GCS ≤ 14 - GCS deterioration ≥ 2 points (1 hour after presentation) - Vomiting - Posttraumatic seizure - Age ≥ 60 year - Clinical signs of skull base fracture [b] - Dangerous trauma mechanism [c] - PTA ≥ 4 hours - Use of anticoagulants, coagulopathy or chronic alcohol abuse - Focal neurologic deficit [a] - Clinical suspicion of intoxication with drugs or alcohol Minor criteria (2 or more than perform a CT) - Persistent anterograde amnesia - Age 40-60 year - Traumatic injury above the clavicula - GCS deterioration with 1 point (1 hour after presentation) - Fall from height < 1m - PTA 2-4 hours - LOC

[a] Neurologic deficit: paresis, dysphasia or other (cranial nerve damage including diplopia, changes in sensibility, asymmetrical reflexes or pathological reflexes, coordination problems and ataxia), [b] Clinical signs of skull base fracture: raccoon eyes, battle sign, hemotympanum, CSF otorrhea, CSF rhinorrhea, palpable discontinuity, bleeding from ear, [c] Dangerous trauma mechanism: pedestrian/cyclist versus vehicle, ejected from vehicle, fall from elevation (more than 1 meter or 5 stairs) or an equivalent mechanism. CT = computed tomography, CHIP = CT in Head Injury Patients, GCS = Glasgow Coma Scale, LOC = loss of consciousness, PTA = posttraumatic amnesia

Chapter 5

The use and clinical consequences of CTA in patients with blunt cerebrovascular injury

In preparation

Kelly A. Foks
Boudewijn Drop
Aad van der Lugt
Iain K. Haitsma
Diederik W.J. Dippel
Adriaan C.G.M. van Es

Part 2

Improving CT decision rules

Chapter 6

External validation of computed tomography decision rules for minor head injury: prospective, multicenter cohort study in the Netherlands.

BMJ 2018

Kelly A. Foks
Crispijn L. van den Brand
Hester F. Lingsma
Joukje van der Naalt
Bram Jacobs
Eline de Jong
Hugo F. den Boogert
Özcan Sir
Peter Patka
Suzanne Polinder
Menno Gaakeer
Charlotte E. Schutte
Kim E. Jie
Huib F. Visee
Myriam G. M. Hunink
Eef Reijners
Meriam Braaksma
Guus Schoonman
Ewout W. Steyerberg
Korné Jellema
Diederik W.J. Dippel

Abstract

Objective: To externally validate four commonly used rules in computed tomography (CT) for minor head injury.

Design: Prospective, multicentre cohort study.

Setting: Three university and six non-university hospitals in the Netherlands.

Participants: Consecutive adult patients aged 16 years and over who presented with minor head injury at the emergency department with a Glasgow coma scale score of 13-15 between March 2015 and December 2016.

Main outcome measures: The primary outcome was any intracranial traumatic finding on CT; the secondary outcome was a potential neurosurgical lesion on CT. The sensitivity, specificity, and clinical usefulness (defined as net proportional benefit, a weighted sum of true positive classifications) of the four CT decision rules. The rules included the CT in head injury patients (CHIP) rule, New Orleans criteria (NOC), Canadian CT head rule (CCHR), and National Institute for Health and Care Excellence (NICE) guideline for head injury.

Results: For the primary analysis, only six centres that included patients with and without CT were selected. Of 4557 eligible patients who presented with minor head injury, 3742 (82%) received a CT scan; 384 (8%) had a intracranial traumatic finding on CT, and 74 (2%) had a potential neurosurgical lesion. The sensitivity for any intracranial traumatic finding on CT ranged from 73% (NICE) to 99% (NOC); specificity ranged from 4% (NOC) to 61% (NICE). Sensitivity for a potential neurosurgical lesion ranged between 85% (NICE) and 100% (NOC); specificity from 4% (NOC) to 59% (NICE). Clinical usefulness depended on thresholds for performing CT scanning: the NOC rule was preferable at a low threshold, the NICE rule was preferable at a higher threshold, whereas the CHIP rule was preferable for an intermediate threshold.

Conclusions: Application of the CHIP, NOC, CCHR, or NICE decision rules can lead to a wide variation in CT scanning among patients with minor head injury, resulting in many unnecessary CT scans and some missed intracranial traumatic findings. Until an existing decision rule has been updated, any of the four rules can be used for patients presenting minor head injuries at the emergency department. Use of the CHIP rule is recommended because it leads to a substantial reduction in CT scans while missing few potential neurosurgical lesions.

Introduction

Minor head injury or mild traumatic brain injury is a common injury increasingly seen in emergency departments.[1,2] Possible causes for this increase are ageing of the population and increased awareness of the potential intracranial complications of minor head injury among general practitioners and paramedics.[3,4] Although the risk of intracranial complications after minor head injury is low, the consequences are important because these patients need close observation and sometimes even neurosurgical intervention.[5] Several clinical decision rules exist that aim to identify those patients with minor head injuries who are at high risk for intracranial complications and need computed tomography (CT) of the head. Examples of frequently used decision rules are: the New Orleans criteria (NOC), Canadian CT head rule (CCHR), and the National Institute for Health and Care Excellence (NICE) guideline for head injury (Supplementary Table 1).[6-8]

The purpose of these rules is to detect all relevant intracranial traumatic lesions while minimising the number of unnecessary CT scans. Relevant lesions are those that need neurosurgical intervention or prolonged clinical observation because of a risk of neurological deterioration. Although the number of patients that present at the emergency departments with minor head injury has increased substantially, the overall incidence of disease specific mortality after head injury has remained fairly stable.[9] An increased number of patients leads to more CT scans, longer waiting times at the emergency department, burden for the patients, radiation risks, and higher costs.[10] The need for reliable CT decision rules for minor head injury to reduce unnecessary CT scans is therefore even more apparent.

Two of the decision rules were developed for patients who had had blunt trauma to the head, had a Glasgow coma scale score of 13-15 at presentation, and had experienced loss of consciousness or post-traumatic amnesia.[6,7] However, these two rules could not be applied to patients who had not experienced loss of consciousness or post-traumatic amnesia.[11,12] Therefore, a new decision rule was developed, the CT in head injury patients (CHIP) rule, which includes patients with and without loss of consciousness or post-traumatic amnesia.[13] The potential reduction of CT scans by use of the CHIP rule was estimated at 23% compared with the scanning of all patients.[13]

The NOC, CCHR, and NICE guidelines were externally validated in previous studies, but there has been no external validation of the CHIP rule, even though this is necessary to determine whether the rule is generally applicable.[14-21] Our aim was to perform an external validation of frequently used CT decision rules for minor head injury (CHIP, NOC, CCHR, and NICE) and compare their performance in a multicentre study in the Netherlands in university and non-university hospitals.

Methods

Study design

We conducted a prospective, multicentre cohort study between March 2015 and December 2016 in the Netherlands. Three university emergency departments (all level 1 trauma centres) and six non-university emergency departments (trauma level 1 (two centres), trauma level 2 (two centres), and trauma level 3 (two centres)) participated in this study. The emergency departments were all situated at an urban location. Institutional ethics and research board approval was obtained and informed consent was waived.

Inclusion criteria were age 16 years and over, presentation within 24 h after blunt trauma to the head, and a Glasgow coma scale score of 13-15 at presentation at the emergency department. Patients with and without loss of consciousness or post-traumatic amnesia were included. We excluded all patients with a Glasgow coma scale score of less than 13, patients younger than 16 years, transferred from other hospitals, or with any contraindication for CT.

Definition of risk factors

Clinical data concerning risk factors for intracranial complications used in the CCHR, NOC, NICE, and CHIP decision rules were collected.[6-8,13] These clinical risk factors were: Age; History of coagulopathy; Use of anticoagulants; Dangerous trauma mechanism (pedestrian/cyclist v vehicle, ejected from vehicle, fall from elevation (>1 m or 5 stairs), or an equivalent mechanism); Fall from any elevation; Loss of consciousness reported by patient or witness; Retrograde amnesia; Post-traumatic amnesia; Headache; Vomiting; Intoxication with drugs or alcohol (history or suggestive findings on examination); Post-traumatic seizure; Glasgow coma scale score on presentation; Significant injury above clavicles; Suspected open or depressed skull fracture; Contusion of skull; Clinical signs of skull base fracture (eg, raccoon eyes, battle sign, haemotympanum, cerebrospinal fluid otorrhea, cerebrospinal fluid rhinorrhea, palpable discontinuity, or bleeding from ear); Neurological deficit (paresis, dysphasia, or other such as cranial nerve damage including diplopia, changes in sensibility, asymmetrical reflexes or pathological reflexes, coordination problems and ataxia); Deterioration in Glasgow coma scale 1 h after presentation.

Main outcome measures

The primary outcome was any (intra)cranial traumatic finding on CT, defined as a subdural haematoma, epidural haematoma, subarachnoid haemorrhage, cerebral lesions (haemorrhagic contusion, non-haemorrhagic contusion, diffuse axonal injury), intraventricular haemorrhage, and skull fracture. The secondary outcome was any potential neurosurgical lesion, which was defined as an intracranial traumatic

finding on CT that could lead to a neurosurgical intervention or death. Examples of potential neurosurgical lesions are an epidural haematoma, large acute subdural haematoma (mass), large contusion(s) (mass), depressed skull fracture, and any lesion with a midline shift or herniation. To compare our findings with previous studies, we also assessed the performance of decision rules for detecting neurosurgical interventions. All outcome measures were chosen a priori.

Study procedures

During patient inclusion in the study, neurologists (in training) and emergency physicians (in training) followed their local guideline for CT scanning in patients with minor head injury. Most participating centres used the same national guideline based on the CHIP rule, two centres followed a slightly adapted guideline (Supplementary Table 2).

Eligible patients were consecutively included by trained researcher physicians, who did not personally interview the patients. Clinical data were collected before diagnostic tests as far as possible by using forms the clinicians could fill in for each patient. The head CT scans were performed according to a routine trauma protocol at each hospital. The scans were interpreted by (neuro)radiologists who were aware of the patient's history and clinical findings, but they were not aware of the actual score of the CT decision rules.

The clinical risk factors were collected by taking the patient's history or information from a witness or family member. Characteristics such as injury severity score were also collected. All patients' details about hospital admission, neurosurgical intervention, and moment of discharge were collected. If the patient was scanned, details about CT findings were recorded. The electronic health records were reviewed 30 days after the injury to assess follow-up information about a neurosurgical intervention. All data were entered by researcher physicians in the case report forms of the web based data management system OpenClinica (LCC, version 3.12.2).

Data management

After patient inclusion and data entering, two authors (KAF and CLvdB) checked the database for correct patient inclusion and completeness of data using IBM statistical package for social sciences (SPSS) version 21. Missing data were assumed to be missing at random; so to avoid bias, missing data were imputed on the basis of all the risk factors mentioned above, using multiple imputation (n=5) with the "multivariate imputation by chained equations" function in R, version 3.3.2 (R foundation for statistical computing).

Data analysis

The study population was described in terms of demographic characteristics, risk factors, admission to the hospital, and neurosurgical intervention. In patients with a CT scan, we also evaluated any intracranial traumatic findings and potential neurosurgical lesions on CT. Continuous variables were described as mean and interquartile range, categorical variables as frequencies and percentages.

The diagnostic performance of the CHIP, NOC, CCHR, and NICE decision rules for detecting intracranial traumatic findings and potential neurosurgical lesions were compared. Because the NOC and CCHR rules were developed in a specific patient population, we performed the analysis in our entire study population, as well as in a subset of the study population (based on the inclusion/exclusion criteria of the development studies of the NOC and CCHR; referred to as original NOC and original CCHR), and in our entire study population with adjustment of the rules. In the adjusted rules, the exclusion criteria of the NOC and CCHR rules were added as additional risk factors (referred to as adjusted NOC and adjusted CCHR). For the NOC rule, a Glasgow coma scale score of 13 or 14 and presence of neurological deficit were added. Finally, for the CCHR rule, use of anticoagulation, post-traumatic seizure, and presence of neurological deficit were added. All patients who had a risk factor according to the NOC or CCHR rules scored positive on these rules, indicating that they needed a CT scan.

The sensitivity, specificity, and proportion of patients needing a CT scan (with 95% confidence intervals) were assessed for each of the four decision rules. Sensitivity was calculated by dividing the number of patients in whom the outcome measure was present and the decision rule was positive, by the total number of patients in whom the outcome measure was present. Specificity was calculated by dividing the number of patients in whom the outcome measure was absent and the decision rule was negative, by the total number of patients in whom the outcome measure was absent. The Cochran's Q test was used to directly compare the sensitivities and specificities between the four decision rules, but it should be noted that results of this test do not automatically imply that any one rule is better than the other.[22] The proportion of patients needing a CT scan was calculated by dividing the number of patients in whom the decision rule was positive by the total number of patients. Confidence intervals were calculated by a bootstrapping method in R, which analyses the performance for each rule 500 times and derived the confidence intervals from the results.

In patients without a CT scan, the outcomes could not be observed. In these patients, the expected outcomes (any intracranial traumatic finding and potential neurosurgical lesion) were imputed on the basis of their risk factors with multiple imputation, in order to avoid selection bias and thus yield unbiased estimates of sensitivity and specificity.[23] This imputation was possible for patients from six of the

nine centres, because the other three centres had not included patients without a CT scan. The patients with and without CT scans (with imputed outcomes) from these six centres were used for the primary analysis. In addition, we analysed all patients with a CT scan from all the centres in a secondary (sensitivity) analysis, which in theory would lead to an overestimation of sensitivity and underestimation of specificity of all the rules.

In this decision problem, avoiding false negatives was more important than avoiding false positives: a false negative result leads to not performing a CT scan and thus potentially misses a lesion, whereas a false positive result leads to performing an unnecessary CT scan. The decision rule should identify all patients with potential neurosurgical lesions and most with intracranial traumatic findings, because of the severe clinical consequences (intracranial surgery, neurological sequelae, death).

Net proportional benefit has been proposed to incorporate such weighting in calculation of clinical usefulness of decision rules.[24,25] For each rule, we expressed the net proportional benefit using the formula: (true positives/total number) - weight×(false positives/total number). Over a range of different weights, the net proportional benefit was calculated and compared with the scanning of all patients. The weight in this formula expresses the ratio of harmful consequences due to a false positive divided by the harmful consequences of a false negative, and it is equivalent to the odds of a lesion above which one would perform a CT scan. At a low threshold for performing CT, we would avoid false negatives of the decision rule (that is, maximise true positives) at the cost of performing many CT scans: if the threshold is 1%, this level implies performing 100 CT scans to avoid one missed lesion. At a higher threshold for performing CT, we would avoid false positives of the decision rule: if the threshold is 10%, this level implies performing 10 CT scans to avoid one missed lesion. We considered an intermediate range of thresholds (4-6% for any traumatic finding and 0.5%-1% for potential neurosurgical lesion) acceptable from a clinical point of view.[24,26] Net proportional benefit expresses the true positives, and the decision rule with the highest net benefit at the intermediate thresholds has the highest clinical value.[24] All statistical analyses were performed with R software, version 3.3.2 (R foundation for statistical computing, Vienna, Austria).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are plans to disseminate the results of the research to the relevant patient community.

Results

Between March 2015 and December 2016, 5839 consecutive patients with minor head injury were entered in the database in the participating centres (Figure 1). After checking the inclusion and exclusion criteria, 322 patients were excluded from the study (Glasgow coma scale score <13, age <16 years, or no blunt head injury). In three of the nine centres, only patients with a CT scan were included (n=960). The remaining six centres included patients with and without a CT scan (n=4557).

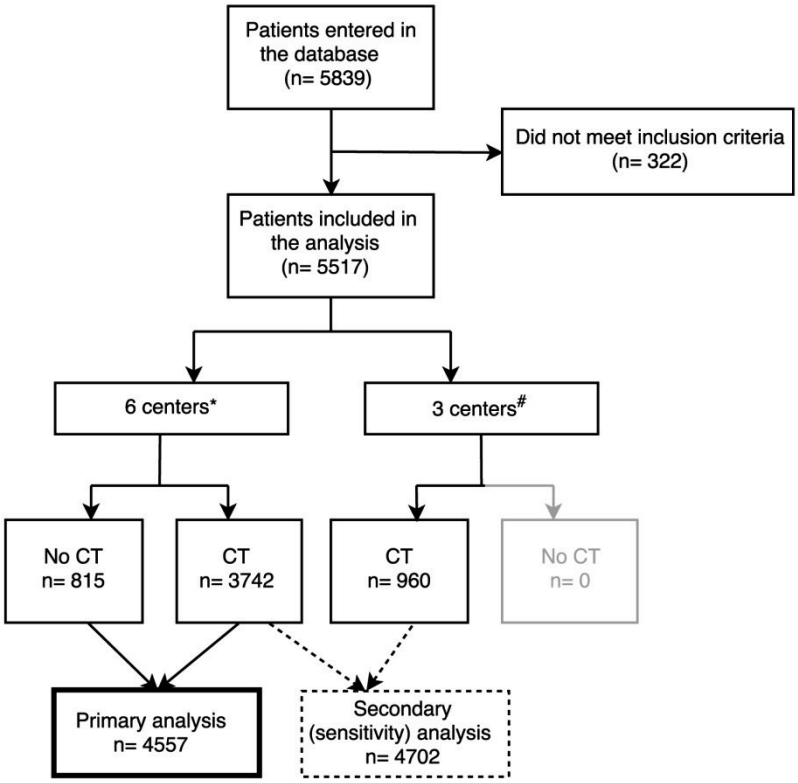


Figure 1. Study flow diagram.
*Six centres=one university centre (trauma level 1) and five non-university centres (trauma levels 1 (two centres), 2 (one), 3 (two)), including patients with and without CT scans; three centres=two university centres (both trauma level 1) and one non-university centre (trauma level 2), including only patients with a CT scan. CT=computed tomography

For the primary analysis, 4557 patients from six centres were included; 3742 (82.1%) received a CT scan and 815 (17.9%) did not. Compared with patients who received

a CT scan, more patients without a scan had a Glasgow coma scale score of 15 (n=3109 (83.1%) v n=805 (98.8%)), and fewer patients experienced loss of consciousness (n=1136 (30.3%) v n=56 (6.8%)) or post-traumatic amnesia (n=1075 (28.7%) v n=29 (3.5%); table 1). Some data were unknown to the including physician, which was most frequently the case for retrograde amnesia (n=675, 14.8%), loss of consciousness (n=651, 14.3%), post-traumatic amnesia (n=502, 11%), and headache (n=630, 13.8%; table 1).

Table 1. Baseline characteristics of 4557 study patients from six centres*

	All patients (n=4557)	Missing	Patients with CT (n=3742)	Patients without CT (n=815)
Age mean in years (range)	53.1 (16-101)	-	56.9 (16-101)	35.7 (16-96)
Sex, n male (%)	2656 (58.3%)	-	2145 (57.3%)	511 (62.7%)
GCS score at presentation		-		
- GCS 13	143 (3.1%)		141 (3.8%)	2 (0.2%)
- GCS 14	500 (11.0%)		492 (13.1%)	8 (1.0%)
- GCS 15	3914 (85.9%)		3109 (83.1%)	805 (98.8%)
Use of anticoagulation		29 (0.6%)		
- None	4045 (88.8%)		3233 (86.4%)	812 (99.6%)
- Coumarin	418 (9.2%)		418 (11.2%)	-
- Direct oral anticoagulants	54 (1.2%)		53 (1.4%)	1 (0.1%)
Use of thrombocyte aggregation inhibitors	615 (13.5%)	33 (0.7%)	577 (15.4%)	38 (4.7%)
Bleeding disorder	44 (1%)	33 (0.7%)	41 (1.1%)	3 (0.4%)
Mechanism of injury		47(1.0%)		
- Road traffic accident Pedestrian	64 (1.4%)		57 (1.5%)	7 (0.9%)
- Road traffic accident Cyclist	162 (3.6%)		152 (4.1%)	10 (1.2%)
- Fall from height	574 (12.6%)		532 (14.2%)	42 (5.2%)
- Other†	3710 (81.4%)		2955 (79.0%)	755 (92.6%)
Ejected from vehicle	150 (3.3%)	56 (1.2%)	135 (3.6%)	15 (1.8%)
Loss of consciousness		651 (14.3%)		
- None	2714 (59.6%)		1968 (52.6%)	746 (91.5%)
- 15 minutes or less	1160 (25.5%)		1105 (29.5%)	55 (6.7%)
- More than 15 minutes	32 (0.7%)		31 (0.8%)	1 (0.1%)
Retrograde amnesia		675 (14.8%)		
- None	3425 (75.2%)		2637 (70.5%)	788 (96.7%)
- 30 minutes or less	312 (6.8%)		303 (8.1%)	9 (1.1%)
- More than 30 minutes	145 (3.2%)		144 (3.8%)	1 (0.1%)
Posttraumatic amnesia		502 (11%)		
- None	2951 (64.8%)		2185 (58.4%)	766 (94.0%)
- Up to 2 hours	976 (21.4%)		948 (25.3%)	28 (3.4%)
- 2-4 hours	69 (1.5%)		68 (1.8%)	1 (0.1%)
- More than 4 hours	59 (1.3%)		59 (1.6%)	-

Intoxication with drugs or Alcohol	1031 (22.6%)	85 (1.9%)	922 (24.6%)	109 (13.4%)
Posttraumatic seizure	36 (0.8%)	68 (1.5%)	33 (0.9%)	3 (0.4%)
Headache	1410 (30.9%)	630 (13.8%)	1208 (32.3%)	202 (24.8%)
Vomiting		50 (1.1%)		
- Once	158 (3.5%)		148 (4.0%)	10 (1.2%)
- Twice or more	144 (3.2%)		142 (3.8%)	2 (0.2%)
GCS deterioration (after 1 hr)		23 (0.5%)		
- 1 point	38 (0.8%)		38 (1.0%)	-
- 2 or more points	12 (0.3%)		12 (0.3%)	-
Neurological deficit‡	130 (2.9%)	141 (3.1%)	128 (3.4%)	2 (0.2%)
Signs of skull base fracture	144 (3.2%)	25 (0.5%)	139 (3.7%)	5 (0.6%)
Visible injury of the head	2564 (56.3%)	19 (0.4%)	2208 (59%)	356 (43.7%)
Visible injury of the face	1631 (35.8%)	22 (0.5%)	1315 (35.1%)	316 (38.8%)
Suspicion of open fracture	11 (0.2%)	40 (0.9%)	11 (0.3%)	-
Injury Severity Score, mean (range)	6.5 (0-75)	-	7.1 (0-75)	3.5 (0-29)

Data are number (%) of patients unless stated otherwise. CT=computed tomography.
*These centres refer to those on the left hand side of figure 1, for the primary analysis.
†Includes patients with mild head injury such as a bumped head against an object.
‡History or suggestive findings on examination (eg, nystagmus, abnormal walking).

In 384 patients (8.4%), CT showed an intracranial traumatic finding, mostly consisting of traumatic subarachnoid haemorrhages (n=182, 4.0%) and skull fractures (n=150, 3.3%; table 2). Of 74 (1.6%) patients with a potential neurosurgical lesion, 18 (0.4%) underwent a neurosurgical intervention for head injury within 30 days after the injury.

In 116 of 3742 patients without loss of consciousness and in 117 of 3742 patients without post-traumatic amnesia, an intracranial traumatic finding was found (table 3). In total, 20 patients without loss of consciousness had a potential neurosurgical lesion and four patients underwent a neurosurgical intervention. In patients without post-traumatic amnesia, 14 had a potential neurosurgical lesion and three underwent a neurosurgical intervention.

In a subgroup analysis of the 3914 patients with a Glasgow coma scale score of 15, more than half the patients (n=2465, 63%) had no loss of consciousness and no post-traumatic amnesia. Ninety three (3.8%) patients had any intracranial traumatic finding, seven (0.3%) had a potential neurosurgical lesion, and one underwent a neurosurgical intervention.

Of all 4557 patients, 1511 (33.2%) were admitted to the hospital for head injury and other reasons. Of the admitted patients, 226 (5.0%) were admitted for two nights or longer because of head injury; 52 (1.1%) had neurological deterioration during admission, and six (0.1%) were intubated for longer than 24 h. Eleven (0.2%) patients died as a result of head injury, and 21 (0.5%) died as a result of a different illness or trauma.

Table 2. Traumatic CT findings in 3742 patients with a CT scan from six centres*

CT finding	N (%)
CT finding†	384 (8.4%)
Skull fracture	150 (3.3%)
Depressed fracture	19 (0.5%)
Linear fracture	66 1.4%)
Skull base fracture	68 (1.5%)
Subarachnoid hemorrhage	182 (4.0%)
Contusion	
Small	115 (2.5%)
Large (mass)	10 (0.2%)
Subdural hematoma	
Small	126 (2.8%)
Large (mass)	22 (0.5%)
Epidural hematoma	
Small	30 (0.7%)
Large (mass)	5 (0.1%)
Suspicion of diffuse axonal injury on CT	13 (0.3%)
Basal cisterns compressed or obliterated	11 (0.2%)
CT shift	
- 0-4mm	16 (0.4%)
- 5mm or more	9 (0.2%)

CT=computed tomography.

*These centres refer to those on the left hand side of figure 1, for the primary analysis.

†Some patients had more than one CT finding.

Table 3. Baseline characteristics of 3742 patients with a CT scan from six centres*, according to status of CT findings

	Normal CT (n=3358)	Abnormal CT (n=384)	All patients with CT (n=3742)
Age mean in years (range)	56.6 (16-101)	59.1 (17-98)	56.9 (16-101)
Sex, n male (%)	1901 (56.6)	244 (63.5%)	2145 (57.3%)
GCS score at presentation			
- GCS 13	94 (2.8%)	47 (12.2%)	141 (3.8%)
- GCS 14	401 (11.9%)	91 (23.7%)	492 (13.1%)
- GCS 15	2863 (85.3%)	246 (64.1%)	3109 (83.1%)
Use of anticoagulation			
- None	2886 (85.9%)	347 (90.4%)	3233 (86.4%)
- Coumarin	387 (11.5%)	31 (8.1%)	418 (11.2%)
- Direct oral anticoagulants	50 (1.5%)	3 (0.8%)	53 (1.4%)
Use of thrombocyte aggregation inhibitors	502 (15.0%)	75 (19.5%)	577 (15.4%)
Bleeding disorder	39 (1.2%)	2 (0.5%)	41 (1.1%)
Mechanism of injury			
- Road traffic accident Pedestrian	48 (1.4%)	9 (2.3%)	57 (1.5%)
- Road traffic accident cyclist	127 (3.8%)	25 (6.5%)	152 (4.1%)
- Fall from height	451 (13.4%)	81 (21.1%)	532 (14.2%)
- Other†	2691 (80.1%)	264 (68.8%)	2955 (79%)
Ejected from vehicle	120 (3.6%)	15 (3.9%)	135 (3.6%)
Loss of consciousness			

- None	1852 (55.2%)	116 (30.2%)	1968 (52.6%)
- 15 minutes or less	943 (28.1%)	162 (42.2%)	1105 (29.5%)
- More than 15 minutes	21 (0.6%)	10 (2.6%)	31 (0.8%)
Retrograde amnesia			
- None	2443 (72.8%)	194 (50.5%)	2637 (70.5%)
- 30 minutes or less	251 (7.5%)	52 (13.5%)	303 (8.1%)
- More than 30 minutes	102 (3.0%)	42 (10.9%)	144 (3.8%)
Posttraumatic amnesia			
- None	2068 (61.6%)	117 (30.5%)	2185 (58.4%)
- Up to 2 hours	776 (23.1%)	172 (44.8%)	948 (25.3%)
- 2-4 hours	54 (1.6%)	14 (3.6%)	68 (1.8%)
- More than 4 hours	38 (1.1%)	21 (5.5%)	59 (1.6%)
Intoxication *	836 (24.9%)	86 (22.4%)	922 (24.6%)
Posttraumatic seizure	26 (0.8%)	7 (1.8%)	33 (0.9%)
Headache	1086 (32.3%)	122 (31.8%)	1208 (32.3%)
Vomiting			
- Once	131 (3.9%)	17 (4.4%)	148 (4.0%)
- Twice or more	119 (3.5%)	23 (6.0%)	142 (3.8%)
GCS deterioration (after 1 hr)			
- 1 point	33 (1.0%)	5 (1.3%)	38 (1.0%)
- 2 or more points	6 (0.2%)	6 (1.6%)	12 (0.3%)
Neurological deficit ‡	100 (3.0%)	28 (7.3%)	128 (3.4%)
Signs of skull base fracture	89 (2.7%)	50 (13.0%)	139 (3.7%)
Visible injury of the head	1945 (57.9%)	263 (68.5%)	2208 (59%)
Visible injury of the face	1181 (35.2%)	134 (34.9%)	1315 (35.1%)
Suspicion of open fracture	6 (0.2%)	5 (1.3%)	11 (0.3%)
Injury Severity Score, mean (range)	6.2 (0-54)	15.2 (1-75)	7.1 (0-75)

Data are number (%) of patients unless stated otherwise. CT=computed tomography.
*These centres refer to those on the left hand side of figure 1, for the primary analysis.
†Includes patients with mild head injury such as a bumped head against an object.
‡History or suggestive findings on examination (eg, nystagmus, abnormal walking).

Performance of the decision rules

After imputation of outcomes in patients without a CT scan, 23 of 815 patients had any intracranial traumatic finding and no patient had a potential neurosurgical lesion. None of these 815 patients without a CT scan had undergone a neurosurgical intervention in 30 days after injury. The sensitivity for identifying patients with any intracranial traumatic finding on CT ranged from 72.5% for the NICE criteria to 98.8% for the NOC rule (table 4, Supplementary Figure 1).

Table 4. Performance of the four decision rules* used for CT in 4557 patients with minor head injury presenting at six centres†

	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)	Positive likelihood ratio (CI)	Negative likelihood ratio (CI)
CHIP n=4557						
Any traumatic finding on CT			94.1 (91.5 to 96.3)	21.6 (20.4 to 22.9)	1.20 (1.16 to 1.23)	0.27 (0.17 to 0.40)
CHIP - Positive	383	3253				
CHIP - Negative	24	897				
Potential neurosurgical lesion			97.3 (93.1 to 100)	20.5 (19.4 to 21.7)	1.22 (1.17 to 1.26)	0.13 (0 to 0.34)
CHIP - Positive	72	3564				
CHIP - Negative	2	919				
NICE n=4557						
Any traumatic finding on CT			72.5 (67.8 to 77.2)	60.9 (59.3 to 62.5)	1.85 (1.72 to 2.0)	0.45 (0.37 to 0.53)
NICE - Positive	295	1624				
NICE - Negative	112	2526				
Potential neurosurgical lesion			85.1 (76.4 to 92.9)	58.6 (57.1 to 60.1)	2.06 (1.84 to 2.27)	0.25 (0.12 to 0.40)
NICE - Positive	63	1856				
NICE - Negative	11	2627				
NOC n=4557						
Any traumatic finding on CT			98.8 (97.6 to 99.8)	4.4 (3.8 to 5.1)	1.03 (1.02 to 1.05)	0.28 (0.06 to 0.53)
NOC - Positive	402	3966				
NOC - Negative	5	184				
Potential neurosurgical lesion			100 (100 to 100)	4.2 (3.6 to 4.8)	1.04 (1.04 to 1.05)	0 (0 to 0)
NOC - Positive	74	4294				
NOC - Negative	0	189				
CCHR n=4557						
Any traumatic finding on CT			80.3 (76.1 to 84.2)	44.2 (42.7 to 45.9)	1.44 (1.35 to 1.52)	0.44 (0.36 to 0.55)
CCHR - Positive	327	2314				
CCHR - Negative	80	1836				
Potential neurosurgical lesion			87.8 (79.7 to 94.9)	42.5 (41.0 to 44.1)	1.53 (1.40 to 1.66)	0.29 (0.12 to 0.47)
CCHR - Positive	65	2576				
CCHR - Negative	9	1907				

*CHIP=CT in head injury patient rule; NICE=National Institute for Health and Care Excellence guideline for head injury; NOC=New Orleans criteria; CCHR=Canadian CT head rule. †These centres refer to those on the left-hand side of figure 1, for the primary analysis.

The sensitivity for identifying patients with potential neurosurgical lesions was 100% for NOC, the NICE criteria had the lowest sensitivity (85.1%) for identifying potential neurosurgical lesions (table 4). The NICE criteria would have missed 11 of 74 patients with potential neurosurgical lesions (Supplementary Table 3). The CHIP criteria would have missed two patients with potential neurosurgical lesions, who both had a small epidural haematoma, which did not need neurosurgical treatment. Of these two missed patients, one had surgery to repair a depressed skull fracture (Supplementary Table 3).

The specificity for identifying any intracranial traumatic finding was lowest for the NOC rule (4.4%) and highest for the NICE criteria (60.9%). The specificity for potential neurosurgical lesions ranged from 4.2% (NOC) to 58.6% (NICE criteria). The sensitivity and specificity differed significantly between all the rules (Cochran's Q $P<0.001$). Sensitivity and specificity for the original CCHR and NOC groups were slightly different from the adjusted versions (see the methods section for definition of the original and adjusted groups; (Supplementary Table 4A,4B). For the outcome of neurosurgical intervention, the NOC rule had the highest sensitivity (100%) and the NICE criteria the highest specificity (58.1%; (Supplementary Table 5).

Clinical usefulness

The decision curve of the NOC rule was almost identical to CT scanning all patients in both study outcomes (Figure 2). When using a low threshold for performing CT (to avoid false negatives of the decision rule), we found that the NOC rule and the scanning of all patients had the highest net proportional benefit. When using a high threshold for performing CT (to avoid false positives), we found that the NICE criteria had the highest net proportional benefit (Figure 2). Over a narrow range of intermediate thresholds, the CHIP criteria had the highest net proportional benefit (0.038-0.054 for intracranial traumatic findings and 0.008-0.012 for potential neurosurgical lesions). For the neurosurgical intervention outcome, the differences in net proportional benefit were small (Supplementary Figure 2).

Proportion of patients needing CT

According to the different decision rules, the proportion of the study population needing CT was 95.9% (95% confidence interval 95.3% to 96.5%) with the NOC rule, 79.8% (78.6% to 80.9%) with the CHIP criteria, 58.0% (56.4% to 59.4%) with the CCHR rule, and 42.1% (40.6% to 43.6%) with the NICE criteria. To increase the sensitivity of the CHIP criteria to the level of the NOC rule, 733 more CT scans would have been needed to identify 19 more patients with intracranial traumatic findings and identify two more patients with a potential neurosurgical lesion.

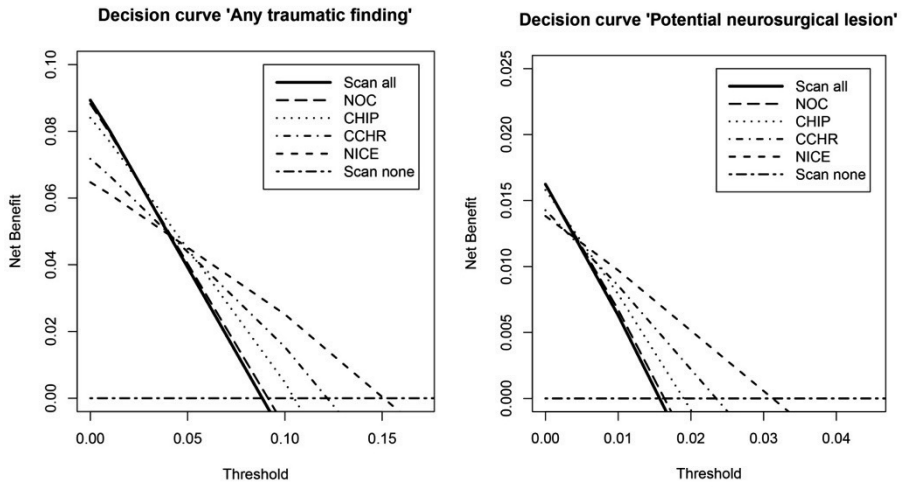


Figure 2. Decision curves for study outcomes showing net proportional benefit per CT decision rule. CT=computed tomography; CHIP=CT in head injury patient rule; NICE=National Institute for Health and Care Excellence guideline for head injury; NOC=New Orleans criteria; CCHR=Canadian CT head rule; scan all=scanning of all patients; scan none=scanning no patients. For each rule, the net proportional benefit was calculated with the formula: (true positives/total number) - weight×(false positives/total number)

Secondary (sensitivity) analysis in all patients receiving CT scans

In all included centres, 4702 patients received a CT scan (fig 1). Most of these patients had a Glasgow coma scale score of 15 at presentation (n=3798; 80.8%), 1511 (32.1%) experienced loss of consciousness, and 1480 (31.5%) had post-traumatic amnesia (Supplementary Table 6A). We found that 528 (11.2%) patients had an intracranial traumatic finding on CT (Supplementary Table 6B). Although the sensitivity of all rules was higher and the specificity lower, their ordering was the same. The NOC rule had the highest sensitivity (99.1%) and lowest specificity (3.1%) for any intracranial traumatic finding, whereas the NICE guideline had the highest specificity (50.3%) and lowest sensitivity (77.5%; Supplementary Figure 3). Net proportional benefit analysis showed the same pattern as in the primary analysis (Supplementary Figure 3).

Discussion

Principal findings

In this large, multicentre, external validation study of CT decision rules for minor head injury patients, the NOC rule had the highest sensitivity and was the only rule with a 100% sensitivity for potential neurosurgical lesions. Nevertheless, the high sensitivity of the NOC rule comes at the cost of an extremely low specificity, with a

consequence that nearly all patients would need a CT scan. The NICE guideline had the highest specificity and the lowest proportion of patients who needed a CT scan, but at the cost of a low sensitivity. The sensitivity of the CHIP criteria was high (97% for potential neurosurgical lesions) with an acceptable specificity and a substantial reduction in the proportion requiring CT. The sensitivity for the identification of patients with any intracranial traumatic finding on CT was less than 100% for all decision rules.

Which decision rule is the best for the situation depends on several factors. It depends not only on its characteristics but also on how many CT scans the physician is willing to perform to identify one patient with an intracranial traumatic finding or potential neurosurgical lesion. Because a potential neurosurgical lesion could have serious consequences, such as a neurosurgical intervention or even death, most professionals would agree that the sensitivity of the decision rule should be 100%.[27] However, it is less easy to agree on the desired sensitivity for finding any intracranial traumatic lesion, because not all small intracranial traumatic findings have clinical consequences. If a CT decision rule gives a false positive result, the patient receives an unnecessary CT scan and will be discharged after spending a few hours in the emergency department. If the rule gives a false negative result, the patient will be discharged without a CT scan and an intracranial traumatic finding will be missed. If this intracranial traumatic finding was a potential neurosurgical lesion and adequate treatment was omitted or was given too late, this missed scan could have serious consequences.[27]

The net proportional benefit analysis might help in finding the best decision rule for different thresholds, but interpretation of the curves can be challenging.[24] If a low threshold is chosen, the best rule to use in order to identify all patients with any lesion is the NOC rule, but this choice would imply that practically all patients undergo CT. At a high threshold, use of the NICE criteria avoids unnecessary scans and has the highest net proportional benefit, but important lesions might be missed. For the outcome of potential neurosurgical lesions, a very low net proportional benefit threshold and 100% sensitivity is desired. For intermediate thresholds, use of the CHIP criteria makes a trade-off between avoiding missed lesions and achieving a substantial reduction in CT scans of 21%. For the outcome of intracranial traumatic findings, the threshold can be higher, because it is not necessary that all findings are identified. From a societal perspective, not only clinical usefulness but also cost effectiveness is important. A cost effectiveness study showed that a prediction rule needs a sensitivity of at least 97% for identifying potential neurosurgical lesions in order to be cost effective, otherwise performing CT in all patients with minor head injury is more cost effective.[26] In our study, only the NOC and CHIP rules fulfilled this criterion.

Comparison with other studies

Several other studies have validated and compared the sensitivity and specificity of CT decision rules for adult patients with minor head injury, but only the NOC, CCHR and NICE decision rules have been externally validated.[13-17,28] Our study adds the CHIP rule to externally validated decision rules and compares it head-to-head with the other rules. Validation studies vary in design and in outcome measures (eg, clinically significant findings on CT are not uniformly defined), and are therefore difficult to compare. In addition, the case mix of our study is different from previous validation studies because we included all patients with blunt traumatic minor head injury, including those without risk factors. Our study is in line with earlier findings that the NOC rule has a high sensitivity but leads to a high scan rate, whereas the CCHR rule and NICE guideline can reduce the number of CT scans substantially, but at the cost of a lower sensitivity. However, the potential reduction in CT scans has not been proved in clinical practice yet. In terms of sensitivity and specificity, the CHIP rule lies between the NOC and CCHR rules.

All the decision rules in this study have been designed for an emergency department population. Although only the NICE and CHIP criteria have been designed to apply to all patients with minor head injury, in daily practice the NOC and CCHR rules probably apply to these patients as well. Therefore, we also investigated adjusted versions of the NOC and CCHR rules, which are applicable to all patients with minor head injury. The sensitivity and specificity of these two adjusted rules were comparable to the sensitivity and specificity of their original versions.

Our study population had a mean age of 53.1 years; by comparison, patients in the development studies for the NOC, CCHR, and CHIP rules had a mean age of 36-41 years. This difference is probably indicative of ageing of the population, as well as other factors such as changes in referral patterns or the increasing incidence of fall accidents.[9] The percentage of patients with any intracranial traumatic finding (8.4%) was comparable with most other studies (6.9-12.1%).[6,7,13] The percentage of patients who underwent a neurosurgical intervention within 30 days after injury in our study (0.4%) was low compared with most other studies (0.4%-1.5%). This difference might be because the indication for neurosurgery not only depends on clinical factors, but also differs from country to country and from neurosurgeon to neurosurgeon and could have changed over time.[29] We therefore believe that instead of actual neurosurgical interventions, it is better to use “potential neurosurgical lesions” as an outcome measure. The confidence intervals for neurosurgical intervention were wide (sensitivity 71-100%) because of the low prevalence of this outcome.

Patients with minor head injury presenting at the emergency department not only reflect the ageing of the population but also the result of the decision rules themselves. In the Netherlands, use of anticoagulants (coumarines or direct oral

anticoagulants) is considered a risk factor for intracranial complications and a reason for referral to the emergency department in both the ambulance and general practitioner protocols.[30] The percentage of patients using anticoagulants in our study was higher than in the CHIP rule development cohort (9.2% v 6.9%).[15]

Limitations of the study

A limitation of our study was that not all consecutive patients with minor head injury were scanned. Following the guidelines for CT scanning at the participating centres resulted in patients with 0-1 minor criteria who did not undergo a CT scan. Therefore, patients who did not receive a CT scan but had intracranial traumatic findings (that is, those with false negative results) could have been missed. To detect this patient subgroup and precisely estimate their relative frequency among unscreened patients would need many thousands of individuals, which was not feasible. Missing patients without a CT scan could have led to a slight overestimation of the sensitivity and an underestimation of the specificity. We therefore performed the primary analysis on data from six centres which also collected data for patients without a CT scan. For all the rules, the new calculated sensitivities were a little lower and the specificities higher, as expected. The fact that most centres in our study used CT guidelines based on the CHIP rule could have introduced a bias in favour of the CHIP rule, owing to possible missed lesions (because the patient was not scanned according to the local guideline) that would have been detected by the other rules. However, by imputing the outcomes of the patients without a CT scan, we were able to keep this bias to a minimum.

Because most physicians used the CHIP rule on a regular basis, they were more likely to apply it correctly. However, many risk factors are the same for all rules and the validation was performed based on the scored risk factors, not on the physicians' judgment of a rule being positive or negative. In addition, in our centres, it is clinical practice to assess not only risk factors from the CHIP rule, but also other risk factors such as headache and retrograde amnesia. In our study, it was unclear how quickly patients proceeded to CT and whether lesions appeared after this time. However, af Geijerstam and colleagues concluded in a literature review that the risk of a patient developing an intracranial lesion after an early normal CT scan is very low.[31]

Another limitation was the possibility that we missed patients undergoing a neurosurgical intervention in a different hospital. However, because the participating centres were all the primary neurosurgery centres of the area, this potential bias is highly unlikely. Furthermore, because we used potential neurosurgical lesions as a secondary outcome instead of neurosurgical intervention, our main findings would not have been affected. In the development studies of the four decision rules, potential neurosurgical lesions were not used as an outcome measure.

Conclusions and policy implications

Application of the CHIP, NOC, CCHR, or NICE decision rules leads to a wide variation in CT scanning among patients with minor head injury, resulting in unnecessary CT scans and missed intracranial traumatic findings. Only the NOC rule did not miss potential neurosurgical lesions, but this was at the cost of having to scan nearly all patients. Although the NICE guideline had the highest reduction of CT scans (58%), missing 15% of patients with potential neurosurgical lesions would be unacceptable to most physicians in the emergency department, because it would mean that for every 200 patients not be scanned according to the NICE criteria, one patient would turn out to have a potential neurosurgical lesion.

Of the four investigated rules, the CHIP rule performed the best with an acceptable sensitivity of 97% for potential neurosurgical lesions according to previous cost effectiveness analysis, the highest net proportional benefit at intermediate thresholds, and a substantial reduction of CT scans of 21% compared with the scanning of all patients. Updating an existing decision rule might increase the sensitivity and specificity for detecting potential neurosurgical lesions. Until this update is conducted, it is justified to use any of the four rules for patients with minor head injury presenting at the emergency department. We recommend use of the CHIP rule because it leads to a substantial reduction of CT scans and misses very few potential neurosurgical lesions.

References

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017;16(12):987-1048.
2. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J Neurotrauma 2016.
3. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 2015;157(10):1683-96.
4. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol 2013;9(4):231-6.
5. af Geijerstam JL, Britton M. Mild head injury - mortality and complication rate: meta-analysis of findings in a systematic literature review. Acta Neurochir (Wien) 2003;145(10):843-50; discussion 50.
6. Haydel MJ, Preston CA, Mills TJ, et al. Indications for computed tomography in patients with minor head injury. N Engl J Med 2000;343(2):100-5.
7. Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. Lancet 2001;357(9266):1391-6.
8. National Clinical Guideline C. National Clinical Guidance Centre. (2014). CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults. . National Institute for Health and Care Excellence 2014.
9. Van den Brand CL, Karger LB, Nijman ST, et al. Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. Eur J Emerg Med 2017.
10. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357(22):2277-84.
11. Smits M, Hunink MG, Nederkoorn PJ, et al. A history of loss of consciousness or post-traumatic amnesia in minor head injury: "conditio sine qua non" or one of the risk factors? J Neurol Neurosurg Psychiatry 2007;78(12):1359-64.
12. Dunning J, Stratford-Smith P, Lecky F, et al. A meta-analysis of clinical correlates that predict significant intracranial injury in adults with minor head trauma. J Neurotrauma 2004;21(7):877-85.
13. Smits M, Dippel DW, Steyerberg EW, et al. Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med 2007;146(6):397-405.
14. Stiell IG, Clement CM, Rowe BH, et al. Comparison of the Canadian CT Head Rule and the New Orleans Criteria in patients with minor head injury. Jama 2005;294(12):1511-8.
15. Smits M, Dippel DW, de Haan GG, et al. External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. Jama 2005;294(12):1519-25.
16. Easter JS, Haukoos JS, Meehan WP, et al. Will Neuroimaging Reveal a Severe Intracranial Injury in This Adult With Minor Head Trauma?: The Rational Clinical Examination Systematic Review. Jama 2015;314(24):2672-81.
17. Harnan SE, Pickering A, Pandor A, et al. Clinical decision rules for adults with minor head injury: a systematic review. J Trauma 2011;71(1):245-51.
18. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart 2012;98(9):691-8.
19. Altman DG, Vergouwe Y, Royston P, et al. Prognosis and prognostic research: validating a prognostic model. Bmj 2009;338:b605.
20. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer 2009.

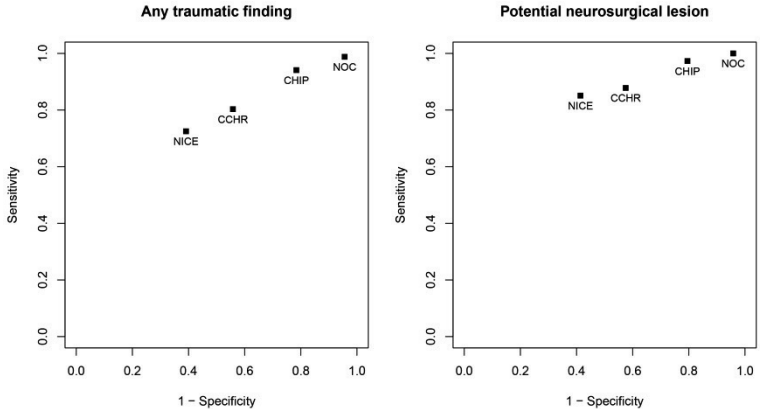
21. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 2016;69:245-7.
22. Leard Statistics. Cochran's Q test using SPSS Statistics. 2018. https://statistics.laerd.com/spss-tutorials/cochrans-q-test-in-spss-statistics.php
23. Sullivan TR, Lee KJ, Ryan P, et al. Multiple imputation for handling missing outcome data when estimating the relative risk. BMC Med Res Methodol 2017;17(1):134.
24. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. Bmj 2016;352:i6.
25. M. Hunink MW, E. Wittenberg, M. Drummond, J. Pliskin, J. Wong,. Decision making in health and medicine: integrating evidence and values. Cambridge University Press, Cambridge 2014.
26. Smits M, Dippel DW, Nederkoorn PJ, et al. Minor head injury: CT-based strategies for management--a cost-effectiveness analysis. Radiology 2010;254(2):532-40.
27. Marincowitz C, Lecky FE, Townend W, et al. The Risk of Deterioration in GCS13-15 Patients with Traumatic Brain Injury Identified by Computed Tomography Imaging: A Systematic Review and Meta-Analysis. J Neurotrauma 2018;35(5):703-18.
28. Bouida W, Marghli S, Souissi S, et al. Prediction value of the Canadian CT head rule and the New Orleans criteria for positive head CT scan and acute neurosurgical procedures in minor head trauma: a multicenter external validation study. Ann Emerg Med 2013;61(5):521-7.
29. 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;34(4):881-89.
30. Batchelor JS, Grayson A. A meta-analysis to determine the effect of anticoagulation on mortality in patients with blunt head trauma. Br J Neurosurg 2012;26(4):525-30.
31. af Geijerstam JL, Britton M. Mild head injury: reliability of early computed tomographic findings in triage for admission. Emerg Med J 2005;22(2):103-7.

Supplementary Table 1. Overview of decision rules CCHR, NOC, CHIP and NICE

Study	Patient population	Indications for CT
NOC: New Orleans Criteria Haydel et al, 2000	GCS score of 15, loss of consciousness, normal findings on brief neurological examination, >3y	Clinical findings: - Headache (diffuse or local) - Vomiting - Age >60 years - Drug or alcohol intoxication - Deficits in short-term memory (persistent anterograde amnesia in patient with otherwise normal GCS) - Physical evidence of trauma above clavicles - Seizure
CCHR: Canadian CT Head Rule Stiell et al, 2001	GCS score 13-15, witnessed LOC, definite amnesia or witnessed disorientation, age >16y Exclusion: use of anticoagulation or obvious open skull fracture	High risk for intervention: - GCS<15 at 2 hours after injury - Suspected open or depressed skull fracture - Any sign of basal skull fracture - Vomiting 2 or more episodes - Age 65 years or older Medium risk for brain injury on CT: - Amnesia before impact 30 min or more - Dangerous mechanism (pedestrian vs vehicle, ejected from vehicle, fall from elevation ≥3 feet, or 5 stairs)
CHIP: CT in Head Injury Patients Smits et al, 2007	GCS 13-14 or GCS of 15 and 1 risk factor, age ≥16	CT indicated if ≥1 major criterion: - Pedestrian or cyclist vs vehicle - Ejected from vehicle - Vomiting - PTA of 4 hours or more - Clinical sign of skull fracture - GCS<15 - GCS deterioration ≥2 points (1hr after presentation) - Use of anticoagulant therapy - Posttraumatic seizure - Age 60 years or older CT indicated if ≥2 minor criteria: - Fall from any elevation - Persistent anterograde amnesia - PTA of 2-4 hours - Contusion of skull - Neurologic deficit - LOC - GCS deterioration of 1 point (1 hour after presentation) - Age 40-60 years
NICE: National Institute for Health and Care Excellence guideline: Head injury	Adults with head injury	Perform CT within 1 hour: - GCS<13 - GCS<15 at 2 hours after injury - Suspected open or depressed skull fracture - Any sign of basal skull fracture - Posttraumatic seizure - Focal neurologic deficit - More than one episode of vomiting since head injury

		Perform CT within 8 hours: - Current warfarin treatment LOC and/or PTA and: - Age >65 years - History bleeding or clotting disorder - Dangerous mechanism of injury - More than 30minutes retrograde amnesia of events before head injury

CT = computed tomography, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia, LOC = loss of consciousness



Supplementary Figure 1. Performance of the CT decision rules (6 centres, n=4557). CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule

Supplementary Table 2. Overview CT guidelines used in participating centres

	National guideline	Local guideline 1	Local guideline 2
Number of centres	7	1	1
1 or more major criteria	- GCS < 15 (including persisting PTA) - 2 or more points deterioration in GCS (1 hour after presentation) - Vomiting - Posttraumatic seizure - Signs of skull fracture - Pedestrian or cyclist versus vehicle - Ejected from motor vehicle - PTA ≥ 4 hours - Use of anticoagulants - Focal neurologic deficit - Suspicion of intracranial injury after focal "high impact" injury	- GCS < 15 - 2 or more points deterioration in GCS (1 hour after presentation) - Vomiting - Posttraumatic seizure - Age ≥60 years - Signs of skull fracture - Dangerous mechanism (Pedestrian or cyclist versus vehicle; Ejected from motor vehicle; Fall from more than 1m or 5 stairs; Or equivalent mechanism) - Post traumatic amnesia ≥ 4 hours - Coagulopathy, e.g. use of coumarin derivate (INR >1.7), NOACs, or chronic alcohol abuse - Focal neurologic deficit - Intoxication that impairs neurological examination	- GCS < 15 (including persisting PTA) - Deterioration in GCS - Vomiting > 1 time - Posttraumatic seizure - Signs of skull fracture - Dangerous mechanism (Pedestrian or cyclist versus vehicle; Ejected from motor vehicle; Fall from high elevation) - Post traumatic amnesia > 1 hour - Use of anticoagulants/coagulopathy - Focal neurologic deficit
2 or more minor criteria	- Fall from any elevation - LOC - Posttraumatic amnesia 2-4 hours - Visible injury to the head, excluding the face (without signs of fracture) - 1 point deterioration in GCS (1 hour post presentation) - Age > 40 years	- Fall from < 1 m - LOC - PTA 2-4 hours - Persisting PTA (recall deficit) - Traumatic injury above the clavicles - 1 point deterioration in GCS (1 hour post presentation) - Age 40-60 years	- Fall from any elevation - LOC - Unclear trauma mechanism - Visible injury to the head, excluding the face (without signs of fracture) - Violence - Age > 65 years

CT = computed tomography, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia, LOC =loss of consciousness, INR = international normalized ratio, NOACS = novel oral anticoagulants

Supplementary Table 3. Overview of missed neurosurgical lesions

	Patient characteristics	CT result	Missed by rule
1	32y, assault blunt instrument, intoxication, significant injury to the head, focal high impact injury	Small EDH, skull fracture	CHIP, NICE, CCHR
2	21y, scooter vs motor vehicle, high energy trauma, significant injury to face and head	Small EDH, small ASDH, skull fracture	CHIP, NICE, CCHR
3	69y, fall from scooter, headache, significant injury to the head	Small EDH	NICE
4	52y, fall from standing height, LOC, PTA, significant injury to the head	Small EDH, tSAH	NICE, CCHR
5	37y, fall from scooter, intoxication, LOC, retrograde amnesia <30 min, PTA 2-4hrs	Small EDH, tSAH, small ASDH	NICE, CCHR
6	26y, forklift against head, LOC, PTA, headache, significant injury to the head, focal high impact injury	Small EDH, tSAH, small ASDH, contusion (small), skull fracture	NICE, CCHR
7	22y, fall from standing height, LOC, retrograde amnesia <30min	Small EDH	NICE, CCHR
8	36y, assault blunt instrument, LOC, PTA, significant injury to the head, focal high impact injury	Small EDH, skull fracture (depressed)	NICE, CCHR
9	88y, scooter vs truck, high energy trauma, significant injury to the head	Small EDH, skull fracture	NICE
10	24y, bicycle vs motor vehicle, high energy trauma, significant injury to the face, LOC, PTA, headache	Small EDH, contusion (small), skull fracture	CCHR
11	40y, bicycle vs bicycle, significant injury to the head, PTA, headache	Small EDH, contusion (small), skull fracture	NICE, CCHR
12	89y, fall from standing height, significant injury to the face	Large ASDH	NICE

CT = computed tomography, EDH = epidural hematoma, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, CCHR = Canadian CT Head Rule ASDH = acute subdural hematoma, LOC = loss of consciousness, PTA = posttraumatic amnesia, tSAH = traumatic subarachnoid hemorrhage

Supplementary Table 4A. NOC and CCHR validation in population with in- and exclusion criteria as in development cohort (6 centres)

	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
Original NOC n=1147 (subset of population with in- and exclusion criteria of original NOC study)				
Any traumatic finding on CT			98.6 (96.4 to 100)	3.5 (2.4 to 4.5)
NOC - Positive	137	973		
NOC - Negative	2	35		
Potential neurosurgical lesion			100 (100 to 100)	3.3 (2.3 to 4.2)
NOC - Positive	20	1090		
NOC - Negative	0	37		
Original CCHR n= 1683 (subset of population with in- and exclusion criteria of original CCHR study)				
Any traumatic finding on CT			81.6 (76.8 to 86.2)	42.5 (39.9 to 45.1)
CCHR - Positive	209	821		
CCHR - Negative	47	606		
Potential neurosurgical lesion			85.1 (74.0 to 94.2)	39.5 (37.2 to 41.9)
CCHR - Positive	40	990		
CCHR - Negative	7	646		

CI = 95% confidence interval, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule, CT= computed tomography

Supplementary Table 4B. Adjusted NOC and adjusted CCHR validation in entire study population (6 centres)

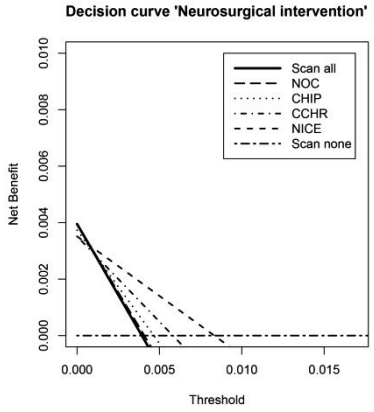
	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
Adjusted NOC n=4557 (including in- and exclusion criteria of original study as risk factors)				
Any traumatic finding on CT			98.8 (97.6 to 99.8)	4.0 (3.4 to 4.5)
NOC - Positive	402	3984		
NOC - Negative	5	166		
Potential neurosurgical lesion			100 (100 to 100)	3.8 (3.2 to 4.3)
NOC - Positive	74	4312		
NOC - Negative	0	171		
Adjusted CCHR n=4557 (including in- and exclusion criteria of original study as risk factors)				
Any traumatic finding on CT			81.8 (77.6 to 85.7)	42.0 (40.4 to 43.6)
CCHR - Positive	333	2409		
CCHR - Negative	74	1741		
Potential neurosurgical lesion			87.8 (79.7 to 94.9)	40.3 (38.9 to 41.7)
CCHR - Positive	65	2677		
CCHR - Negative	9	1806		

CI = 95% confidence interval, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule, CT= computed tomography

Supplementary Table 5. Performance of rules with outcome neurosurgical intervention (6 centres)

	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
CHIP n=4557				
Neurosurgical intervention			94.4 (81.8 to 100)	20.3 (19.2 to 21.4)
CHIP - Positive	17	3619		
CHIP - Negative	1	920		
NICE n=4557				
Neurosurgical intervention			88.9 (71.4 to 100)	58.1 (56.6 to 59.6)
NICE - Positive	16	1903		
NICE - Negative	2	2636		
NOC n=4557				
Neurosurgical intervention			100 (100 to 100)	4.2 (3.6 to 4.7)
NOC - Positive	18	4350		
NOC - Negative	0	189		
CCHR n=4557				
Neurosurgical intervention			88.9 (71.4 to 100)	42.2 (40.7 to 43.8)
CCHR - Positive	16	2625		
CCHR - Negative	2	1914		

CI = 95% confidence interval, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule



Supplementary Figure 2. Decision curves showing net benefit for the outcome neurosurgical intervention. CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule. Per rule net benefit was calculated using the formula: (true positives/n) – weight*(false positives/n).

Supplementary Table 6A. Baseline characteristics all patients with a CT scan (9 centres, n =4702)

	Normal CT (n=4174)	Abnormal CT (n=528)	All patients with CT (n=4702)
Age mean in years (range)	55.5 (16-101)	58.6 (16-98)	55.9 (16-101)
Sex, n male (%)	2372 (56.8%)	337 (63.8%)	2709 (57.6%)
GCS score at presentation			
- 13	138 (3.3%)	69 (13.1%)	207 (4.4%)
- 14	557 (13.3%)	140 (26.5%)	697 (14.8%)
- 15	3479 (83.3%)	319 (60.4%)	3798 (80.8%)
Use of anticoagulation			
- None	3581 (85.8%)	474 (89.8%)	4055 (86.2%)
- Coumarin	490 (11.7%)	45 (8.5%)	535 (11.4%)
- NOACS	56 (1.3%)	3 (0.6%)	59 (1.3%)
Bleeding disorder	47 (1.1%)	3 (0.6%)	50 (1.1%)
Mechanism of injury			
- RTA pedestrian	60 (1.4%)	12 (2.3%)	72 (1.5%)
- RTA cyclist	164 (3.9%)	36 (6.8%)	200 (4.3%)
- Fall from height	574 (13.8%)	124 (23.5%)	698 (14.8%)
- Other	3325 (79.7%)	348 (65.9%)	3673 (78.1%)
Ejected from vehicle	183 (4.4%)	32 (6.1%)	215 (4.6%)
LOC			
- None	2192 (52.5%)	153 (29.0%)	2345 (49.9%)
- 15 minutes or less	1238 (29.7%)	225 (42.6%)	1463 (31.1%)
- More than 15 minutes	30 (0.7%)	18 (3.4%)	48 (1.0%)
Retrograde amnesia			
- None	2819 (67.5%)	227 (43.0%)	3046 (64.8%)
- 30 minutes or less	445 (10.7%)	96 (18.2%)	541 (11.5%)
- More than 30 minutes	142 (3.4%)	58 (11.0%)	200 (4.3%)
PTA			
- None	2456 (58.8%)	154 (29.2%)	2610 (55.5%)
- Up to 2 hours	970 (23.2%)	200 (37.9%)	1170 (24.9%)
- 2-4 hours	80 (1.9%)	22 (4.2%)	102 (2.2%)
- More than 4 hours	144 (3.4%)	64 (12.1%)	208 (4.4%)
Intoxication *	1075 (25.8%)	117 (22.2%)	1192 (25.4%)
Post-traumatic seizure	31 (0.7%)	11 (2.1%)	42 (0.9%)
Headache	1358 (32.5%)	184 (34.8%)	1542 (32.8%)
Vomiting			
- Once	173 (4.1%)	27 (5.1%)	200 (4.3%)
- Twice or more	161 (3.9%)	35 (6.6%)	196 (4.2%)
GCS deterioration			
- 1 point	35 (0.8%)	6 (1.1%)	41 (0.9%)
- 2 or more points	9 (0.2%)	9 (1.7%)	18 (0.4%)
Neurological deficit	104 (2.5%)	29 (5.5%)	133 (2.8%)
Signs of skull base fracture	109 (2.6%)	77 (14.6%)	186 (4.0%)
Visible injury of the head	2237 (53.6%)	338 (64.0%)	2575 (54.8%)
Visible injury of the face	1420 (34.0%)	178 (33.7%)	1598 (34.0%)
Suspicion of open fracture	8 (0.2%)	17 (3.2%)	25 (0.5%)
ISS, mean (range)	6.5 (0-54)	15.3 (1-75)	7.5 (0-75)

CT = computed tomography, GCS = Glasgow Coma Scale, NOACS = novel oral anticoagulants, RTA= road traffic accident, LOC = loss of consciousness, PTA = posttraumatic amnesia, ISS = Injury Severity Score
*history or suggestive findings on examination (for example nystagmus, abnormal walking, etc.)
**GCS deterioration 2 hrs after presentation

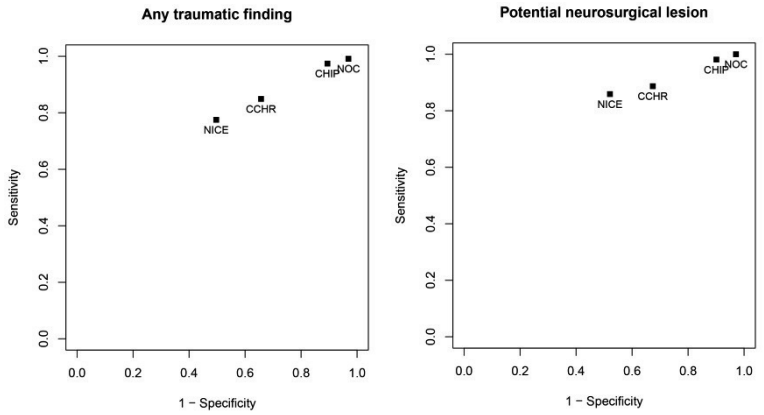
Supplementary Table 6B. Traumatic CT findings all patients with a CT scan (9 centres, n=4702)

CT finding	N (%)
CT finding	528 (11.2%)
Skull fracture	213 (4.5%)
- Depressed fracture	25 (0.5%)
- Linear fracture	103 (2.2%)
- Skull base fracture	89 (1.8%)
Subarachnoid hemorrhage	266 (5.7%)
Contusion	
- Small	154 (3.3%)
- Large (mass)	14 (0.3%)
Subdural hematoma	
- Small	173 (3.7%)
- Large (mass)	27 (0.6%)
Epidural hematoma	
- Small	47 (1.0%)
- Large (mass)	5 (0.1%)
Suspicion of DAI on CT	14 (0.3%)
Basal cisterns compressed or obliterated	13 (0.3%)
CT shift	
- 0-4mm	22 (0.5%)
- 5mm or more	13 (0.3%)

CT = computed tomography, DAI = diffuse axonal injury
*some patients had more than 1 CT finding

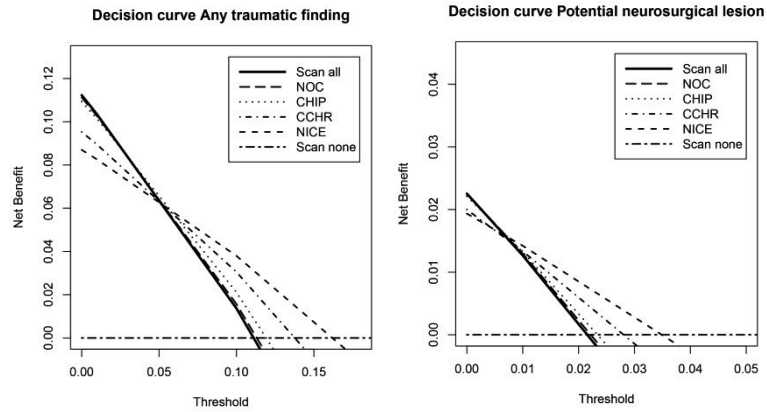
Supplementary Figure 3. Figures additional analysis all patients with a CT (9 centres, n=4702)

I. Performance CT decision rules



CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule

II. Decision curves showing net benefit per decision rule



CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule. Per rule net benefit was calculated using the formula: (true positives/n) – weight*(false positives/n).

Chapter 7

Risk of intracranial complications in minor head injury: the role of loss of consciousness and posttraumatic amnesia in a multicenter observational study.

Journal of Neurotrauma 2019

Kelly A. Foks
Simone A. Dijkland
Hester F. Lingsma
Suzanne Polinder
Crispijn L. van den Brand
Korné Jellema
Bram Jacobs
Joukje van der Naalt
Özcan Sir
Kim E. Jie
Guus Schoonman
Myriam G.M. Hunink
Ewout W. Steyerberg
Diederik W.J. Dippel

Abstract

Various guidelines for minor head injury focus on patients with a Glasgow Coma Scale (GCS) score of 13–15 and loss of consciousness (LOC) or post-traumatic amnesia (PTA), while clinical management for patients without LOC or PTA is often unclear. We aimed to investigate the effect of presence and absence of LOC or PTA on intracranial complications in minor head injury. A prospective multi-center cohort study of all patients with blunt head injury and GCS score of 15 was conducted at six Dutch centers between 2015 and 2017. Five centers used the national guideline and one center used a local guideline—both based on the CT in Head Injury Patients (CHIP) prediction model—to identify patients in need of a computed tomography (CT) scan. We studied the presence of traumatic findings and neurosurgical interventions in patients with and without LOC or PTA. In addition, we assessed the association of LOC and PTA with traumatic findings with logistic regression analysis and the additional predictive value of LOC and PTA compared with other risk factors in the CHIP model. Of 3914 patients, 2249 (58%) experienced neither LOC nor PTA and in 305 (8%) LOC and PTA was unknown. Traumatic findings were present in 153 of 1360 patients (11%) with LOC or PTA and in 67 of 2249 patients (3%) without LOC and PTA. Five patients without LOC and PTA had potential neurosurgical lesions and one patient underwent a neurosurgical intervention. LOC and PTA were strongly associated with traumatic findings on CT, with adjusted odds ratios of 2.9 (95% confidence interval [CI] 2.2–3.8) and 3.5 (95% CI 2.7–4.6), respectively. To conclude, patients who had minor head injury with neither LOC nor PTA are at risk of intracranial complications. Clinical guidelines should include clinical management for patients without LOC and PTA, and they should include LOC and PTA as separate risk factors rather than as diagnostic selection criteria.

Introduction

For minor head injury, several clinical guidelines and Head injury is a common injury seen at emergency departments, comprising mostly (~90%) patients with minor head injury.[1,2] Besides minor head injury, various other definitions are used, such as mild traumatic brain injury, minor traumatic brain injury, or mild head injury.[3] Key components of these definitions are blunt traumatic injury to the head, a Glasgow Coma Scale (GCS) score of 13–15 on admission, and often loss of consciousness (LOC) or post-traumatic amnesia (PTA).[4,5]

Several decision rules have been developed to help decide which patients are at higher risk of intracranial complications and need a computed tomography (CT) of the head.[6–9] Some of these clinical guidelines were only developed for patients with LOC or PTA, while for patients without LOC or PTA no scan recommendation was provided, or clinicians were simply advised to discharge the patients to home without a CT (Table 1).[10–13] However, it is likely that the absence of LOC and PTA does not exclude the possibility of intracranial traumatic findings, including a subdural and epidural hematoma. In many emergency departments only guidelines for patients with LOC or PTA are used, which may lead to discharge of high-risk patients without CT.[14] Moreover, LOC and PTA are known risk factors for intracranial traumatic findings, but have not been added as separate risk factors in some clinical guidelines (Table 1).[11,12,15,16] We hypothesize that although LOC and PTA are important risk factors for intracranial complications, patients without LOC and PTA are still at risk of intracranial complications. Therefore, the aim of our study is to investigate the effect of absence and presence of LOC and PTA on intracranial complications in a prospective multi-center study in the Netherlands.

Methods

Study design and setting

Data were prospectively collected in six emergency departments in the Netherlands between 2015 and 2017.[17] The six centers included one university center (trauma Level 1) and five non-university centers (trauma Level 1 [two centers], trauma Level 2 [one center], trauma Level 3 [two centers]). All centers had an urban location. We obtained institutional ethics and research board approval and informed consent was waived.

Inclusion and exclusion criteria

Consecutive patients with blunt traumatic head injury were included if they met the following criteria: presentation within 24 h after blunt trauma to the head, a GCS score of 15 at presentation at the emergency department, and age 16 years and older. All patients with a GCS score of 13–14 were excluded because clinical guidelines will recommend the performance of a head CT regardless of the presence of other

risk factors. Patients with and without a head CT were included. All patients transferred from other hospitals were excluded.

Table 1. Guideline recommendations for CT of patients with and without LOC and PTA

Guideline/ Decision rule	Patients with LOC	Patients with PTA	Patients without LOC	Patients without PTA
American College of Emergency Physicians guideline for mild traumatic brain injury[9]	Other risk factor	Other risk factor	Other risk factor	Other risk factor
Canadian CT Head Rule (CCHR), 2001[10]	Other risk factor	Other risk factor	No recommen-dation*	No recommen-dation*
CT in Head Injury Patients (CHIP), 2007[7]	Other risk factor	- If PTA > 4hrs - If PTA 2-4hrs: if other risk factor - If persistent amnesia: if other risk factor	Other risk factor	Other risk factor
European Federation of Neurological Societies (EFNS) guideline TBI, 2012[27]	Always CT	Always CT	Other risk factor	Other risk factor
National Institute for Health and Care Excellence: Head injury (NICE), 2014[8]	Other risk factor	Other risk factor	Other risk factor	Other risk factor
National Emergency X-Radiography Utilization Study (NEXUS) head CT, 2005[16]	Other risk factor	Abnormal level of alertness including disorientation	Other risk factor	Other risk factor
NCWFNS guideline for mild head injury, 2001[13]	Always CT	Always CT	No CT	No CT
New Orleans Criteria (NOC), 2000[11]	Other risk factor	Deficits in short-term memory and LOC	No recommen-dation#	No recommen-dation
Ono, 2007[19]	LOC or PTA	LOC or PTA	Other risk factor	Other risk factor
Scandinavian guidelines TBI, 2013[12]	If LOC and abnormal S100B	No CT	Other risk factor	Other risk factor

Other risk factor: any other risk factor which will lead to performing a head CT, for example vomiting or use of anticoagulation. CT = computed tomography, GCS = Glasgow Coma Scale, LOC = loss of consciousness, PTA = posttraumatic amnesia, NCWFNS = Neurotraumatology Commity of the World Federation of Neurosurgical Societies, S100B = S100 calcium binding protein (biomarker for head injury)
* CCHR was only developed for patients with witnessed LOC, definite amnesia or witnessed disorientation

Definition of risk factors
Information about risk factors for intracranial complications included in the CT in Head Injury Patients (CHIP) prediction rule were collected as follows: LOC reported by the patient or witness, PTA reported by the patient, the witness or tested at neurological examination, age in years, trauma mechanism (pedestrian or cyclist versus vehicle, ejected from vehicle and fall from any elevation), vomiting, signs of a skull base fracture (for example: raccoon eyes, battle sign, cerebrospinal fluid otorrhea, palpable discontinuity, bleeding from ear), GCS score deterioration (1 or more points) within 1 h after presentation, use of pre-injury anticoagulants, post-traumatic seizure, visible injury to the head (excluding the face), neurological deficit (paresis, dysphasia or other such as cranial nerve damage including diplopia, changes in sensibility, asymmetrical reflexes or pathological reflexes, coordination problems, and ataxia).[7] In addition, information about retrograde amnesia and intoxication with drugs or alcohol (history or suggestive findings on examination, such as symmetrical nystagmus, foetor) was collected.

Outcome measures
The primary outcome was any (intra)cranial traumatic finding on CT, including skull fractures, subdural hematomas, epidural hematomas, subarachnoid hemorrhages, cerebral contusions, suspicion of diffuse axonal injury (at least one petechial hemorrhage), and intraventricular hemorrhages. Secondary outcomes were a 1) neurosurgical intervention within 30 days after the injury and 2) any potential neurosurgical lesion, such as epidural hematomas, large acute subdural hematomas (or mass lesions), large contusions (or mass lesions), depressed skull fractures or any lesion with a midline shift or herniation.

Data collection
All eligible patients were included by trained research physicians and the risk factors were collected by taking the patients' history or information from a witness or family member. The local guidelines were used to assess which patients needed a head CT.[17] Five centers used the national guideline and one center used a local guideline, both based on the CHIP prediction model, to identify patients in need of a CT (Supplementary Table 1). Only the initial head CT was interpreted by (neuro)radiologists for traumatic findings. To ensure accuracy, a subset of CTs were over-read by neuroradiologists. Research physicians reviewed the electronic health records 30 days after the injury to assess information about neurosurgical interventions. All data were entered in the web-based application OpenClinica (LCC, Version 3.12.2).

Statistical analysis

Patients were categorized based on the LOC and PTA variables: all patients with LOC, with PTA, or both were selected for the group "with LOC or PTA." All patients without LOC and PTA were selected for the group "without LOC and PTA." All patients with unknown LOC and PTA were selected for the group "unknown LOC and PTA."

Demographic characteristics, risk factors, and outcome were described using frequencies and percentages for categorical variables, and median and interquartile range for continuous variables.

We performed univariable logistic regression analysis to quantify the relevance of LOC and PTA as individual risk factors for the presence of intracranial traumatic findings on CT and presented the odds ratios (ORs) and 95% confidence intervals (CIs). In addition, we performed multivariable logistic regression analysis to assess the incremental value of LOC and PTA in addition to other risk factors for intracranial traumatic CT findings present in the CHIP prediction model. The CHIP model consisted of the following variables: LOC, PTA, age, pedestrian or cyclist versus vehicle, ejected from vehicle, vomiting, signs of skull fracture, GCS score deterioration, use of anticoagulants, seizure, fall from any elevation, visible injury to the head and neurologic deficit. Four separate models were created: 1) CHIP model without LOC and PTA; 2) CHIP model with LOC; 3) CHIP model with PTA; and 4) complete CHIP model (including LOC and PTA as separate variables). We compared the variability in outcome explained by the variables by Nagelkerke R2 values of the four models.[18]

For univariable and multivariable analysis, missing data (2.4%) were assumed to be missing at random and imputed based on the available data of all nine centers in the original study using multiple imputation (m = 5) with the mice package in R. For patients without a head CT, the expected outcomes (intracranial traumatic finding and potential neurosurgical lesion) were imputed based on their risk factors using multiple imputation.[17] All analyses were performed with R, version 3.3.2 (R foundation for statistical computing, Vienna, Austria).

Results

During the study period, 4557 consecutive patients with blunt traumatic head injury were seen at the six emergency departments. After excluding 643 patients with a GCS score of 13–14 at presentation, we analyzed 3914 minor head injury patients with a GCS score of 15.

LOC and PTA

LOC lasted less than 15 min in 962 patients (n = 962/3914; 25%) and in 24 patients (n = 24/3914; 1%) it lasted 15 min or more. LOC was not documented or unknown in 408 patients (n = 408/3914; 10%). Most patients with PTA had post-traumatic

amnesia for less than 2 h (n = 745/3914; 19%), 40 patients (n = 40/3914; 1%) between 2 and 4 h, and 31 patients (n = 31/3914; 1%) for more than 4 h. The majority of patients did not experience LOC (n = 2520/3914; 64%) or PTA (n = 2816/3914; 72%). PTA was not documented or unknown in 282 patients (n = 282/3914; 7%).

Baseline characteristics

Of all patients, 1360 (n = 1360/3914; 35%) had LOC or PTA, 2249 (n = 2249/3914; 58%) had no LOC and PTA, and 305 patients (n = 305/3914; 8%) had unknown LOC and PTA (Fig. 1).

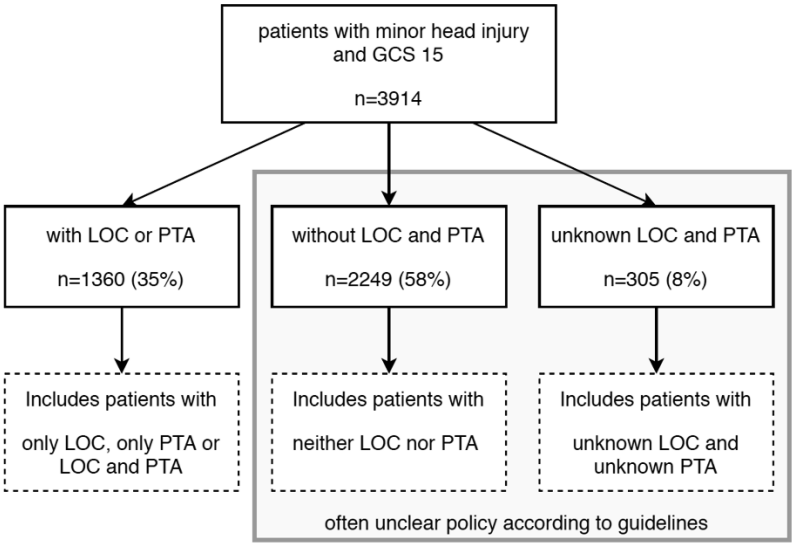


Figure 1. Flowchart patient categorization
GCS = Glasgow Coma Scale, LOC = loss of consciousness, PTA = post traumatic amnesia

The patients with LOC or PTA were slightly younger than the patients without LOC and PTA (median 50.5 vs. median 53 years; Table 2). More patients without LOC and PTA used anticoagulants before the injury than patients with LOC or PTA (n = 227/2249; 12% vs. n = 105/1360; 8%). Patients with LOC or PTA were more often intoxicated with alcohol or drugs (n = 351/1360; 26% vs. n = 284/2249; 13%) and vomited (n = 133/1360; 10% vs. n = 82/2249; 4%) more often than patients without LOC and PTA.

Table 2. Baseline characteristics

	All patients (n=3914)	With LOC or PTA (n=1360)	Without LOC and PTA (n=2249)	Unknown LOC and PTA (n=305)
Demographics				
Age in years, median (IQR)	53 (30-73)	50.5 (29-68)	53 (31-75)	62 (38-79)
Sex, n male	2241 (57%)	814 (60%)	1247 (55%)	180 (59%)
Use of anticoagulants[a]	421 (11%)	105 (8%)	277 (12%)	39 (13%)
Injury descriptives				
Mechanism of injury[b]				
- Pedestrian or cyclist vs vehicle	106 (3%)	38 (3%)	50 (2%)	18 (6%)
- Road traffic accident vehicle or motor	410 (11%)	125 (9 %)	250 (11%)	35 (12%)
- Fall from height	574 (15%)	220 (16%)	302 (13%)	52 (17%)
- Fall from standing	1574 (40%)	584 (43%)	905 (40%)	85 (28%)
- Assault	432 (11%)	154 (11%)	238 (11%)	40 (13%)
- Other*	790 (20%)	219 (16%)	503 (22%)	68 (22%)
Ejected from vehicle[c]	127 (3%)	48 (4%)	69 (3%)	10 (3%)
Fall from any elevation[d]	743 (19%)	310 (23%)	384 (17%)	49 (16%)
Intoxication with drugs or alcohol[e]	758 (19%)	351 (26%)	284 (13%)	123 (40%)
Symptoms				
Retrograde amnesia[f]	339 (9%)	300 (22%)	15 (1%)	24 (8%)
Vomiting[g]	240 (6%)	133 (10%)	82 (4%)	25 (8%)
Neurological deficit[h] **	94 (2%)	40 (3%)	49 (2%)	5 (2%)
Seizure[i]	27 (1%)	22 (2%)	4 (0.2%)	1 (0.3%)
Visible injury of the head[j]	2202 (56%)	756 (56%)	1267 (56%)	179 (59%)
Signs of skull fracture[k]	102 (3%)	49 (4%)	45 (2%)	8 (3%)
GCS score deterioration[l #]	11 (0.3%)	9 (1%)	2 (0.1%)	-

IQR = interquartile range, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia, LOC = loss of consciousness

[a] missing n=13; 0.3%, [b] missing n=28; 1%, [c] missing n=42; 1%, [d] missing n=22; 1%, [e] missing n=66; 2%, [f] missing n=386; 10%, [g] missing n=38; 1%, [h] missing n=128; 3%, [i] missing n=42; 1%, [j] missing n=19; 1%, [k] missing n=20; 1%, [l] missing n=15; 0.4% * includes patients with mild head injury such as bump head against object. ** history or suggestive findings on examination (for example nystagmus, abnormal walking, etc.). [#] GCS deterioration (1 or more points) 1 hour after presentation at the emergency

Outcome

Most patients underwent a head CT (n = 3109/3914; 79%) and 246 patients (n = 246/3914; 6%) had a traumatic intracranial finding on CT, mostly traumatic subarachnoid hemorrhage (n = 111/3914; 3%) or an acute subdural hematoma (n = 91/3914; 2%; Table 3). A potential neurosurgical lesion was found in 32 patients (n = 32/3914; 1%) and eight patients (n = 8/3914; 0.2%) underwent a neurosurgical intervention.

Table 3. Primary and secondary outcomes

Outcome	All patients (n=3914)	With LOC or PTA (n=1360)	Without LOC and PTA n=2249)	Unknown LOC and PTA (n=305)
CT performed	3109 (79%)	1285 (95%)	1531 (68%)	293 (96%)
Traumatic findings on CT	246 (6%)	153 (11%)	67 (3%)	26 (9%)
Skull fracture	82 (2%)	51 (4%)	25 (1%)	6 (2%)
- linear skull fracture	46 (1%)	31 (2%)	12 (1%)	3 (1%)
Epidural hematoma	18 (1%)	13 (1%)	5 (0.2%)	-
Acute subdural hematoma	91 (2%)	56 (4%)	23 (1%)	12 (4%)
Contusion	68 (2%)	46 (3%)	14 (1%)	8 (3%)
Subarachnoid hemorrhage	111 (3%)	82 (6%)	20 (1%)	9 (3%)
Potential neurosurgical lesion	32 (1%)	26 (2%)	5 (0.2%)	1 (0.3%)
Neurosurgical intervention	8 (0.2%)	7 (1%)	1 (0.0%)	-

CT = computed tomography, PTA = posttraumatic amnesia, LOC = loss of consciousness

Almost 70% of the patients without LOC and PTA (n = 1531/2249; 68%) underwent a head CT and 67 patients (n = 67/2249; 3%) had intracranial traumatic findings (Table 3). These 67 patients had a median age of 74 years (interquartile range 44.5–84.0 years), 12 patients (n = 12/67; 18%) used anticoagulation and 10 patients (n = 10/67; 15%) were intoxicated with drugs or alcohol. Two patients vomited twice or more (2/67; 3%) and one patient had a post-traumatic seizure. Three patients had signs of a skull base fracture (n = 3/67; 5%), two patients had a new neurological deficit (n = 2/67; 3%), and 45 patients had a visible injury to the head (45/67; 67%). Five patients (n = 5/2249; 0.2%) had a potential neurosurgical lesion; all had a small epidural hematoma, and one patient also had a depressed skull fracture. One patient (n = 1/2249; 0.0%) underwent a neurosurgical intervention because of a depression fracture and a small epidural hematoma.

Of the 305 patients with unknown LOC and PTA, the majority underwent a head CT (n = 293/305; 96%). In 26 patients (n = 26/305; 9%) intracranial traumatic findings were found and one patient (n = 1/305; 0.3%) had a potential neurosurgical lesion, a large acute subdural hematoma (Table 3).

No other risk factors

There were 42 (n = 42/1360; 3%) patients with LOC or PTA who did not have other risk factors of the CHIP model for intracranial abnormalities and none of these patients had intracranial traumatic findings on CT. There were 69 (n = 69/2249; 3%) patients without LOC and PTA who did not have other risk factors of the CHIP model. Of these, one patient (n = 1/2249; 0.04%) had an intracranial traumatic finding on CT (a small contusion), and none had potential neurosurgical lesions or underwent a neurosurgical intervention. Eight patients (n = 8/305; 3%) with unknown

LOC and PTA had no other risk factors of the CHIP model, and none of these patients had intracranial traumatic findings on CT.

Predictive value of LOC and PTA

Univariable logistic regression analysis for the association between LOC and an intracranial traumatic finding on CT yielded an OR of 3.0 (95% CI 2.4–3.9; Table 4). For PTA, the OR was 3.8 (95% CI 2.9–4.9). For LOC and PTA, the OR was 4.1 (95% CI 3.1–5.3). Multivariable logistic regression analysis for the association between LOC and an intracranial traumatic finding on CT yielded an adjusted OR of 2.9 (95% CI 2.2–3.8). For PTA, the adjusted OR was 3.5 (95% CI 2.7–4.6).

In multivariable logistic regression analysis, the CHIP prediction model without LOC and PTA had a R2 of 6%. The CHIP model with addition of LOC as a predictor had a R2 of 10% and with the addition of PTA as a predictor a R2 of 12% (Fig. 2). After adding both LOC and PTA as predictors, the R2 increased to 13% (Fig. 2).

Table 4. Univariable analysis of LOC and PTA for identification of traumatic findings on CT

Variable	Number of patients	Number of patients with traumatic finding	Odds Ratio (95% CI)
LOC	1184	147	3.0 (2.4-3.9)
PTA	904	135	3.8 (2.9-4.9)
LOC or PTA	1449	172	3.3 (2.5-4.3)
LOC and PTA	639	110	4.1 (3.1-5.3)
No LOC, no PTA	2465	97	0.3 (0.2-0.4)

Calculated after imputation of missing data.

PTA = posttraumatic amnesia, LOC = loss of consciousness, CI = confidence interval

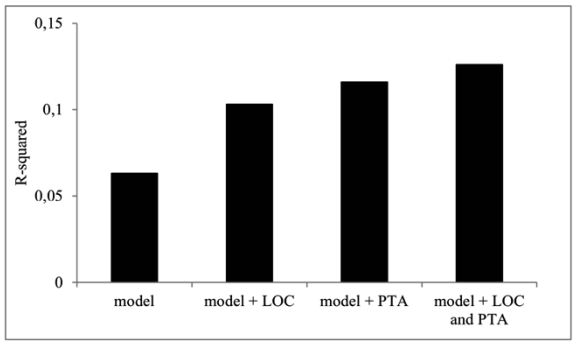


Figure 2. Cumulative prognostic value of LOC and PTA in multivariable logistic regression analysis for identification of traumatic findings on CT.

R-squared = the proportion of variability in outcome explained by the variables. Calculated after imputation of missing data.

Model: traumatic findings on CT ~ age + pedestrian or cyclist versus vehicle + ejected from vehicle + vomiting + signs of skull fracture + GCS score deterioration + use of anticoagulants + seizure + fall from any elevation + visible injury to the head + neurologic deficit. Model +LOC and PTA is the CHIP prediction rule.

Discussion

In this study of patients with blunt traumatic head injury and a GCS score of 15, we confirmed that both LOC and PTA are important risk factors for identifying traumatic intracranial findings on CT. Nevertheless, among more than half of the patients who did not experience LOC and PTA, a small proportion had traumatic intracranial findings on CT and one patient underwent a neurosurgical intervention. Almost all patients with unknown LOC and PTA underwent a head CT and in a small portion, traumatic intracranial findings were found.

Our study shows a strong association of LOC and PTA with traumatic findings on CT. In previous studies, univariable logistic regression analyses yielded ORs for LOC between 1.9 and 6.5 and for PTA between 1.7 and 6.3.[7,15,19–21] Because these studies all used different inclusion criteria and definitions of outcome and variables, the associations are difficult to compare head to head. However, these studies all show that LOC and PTA should be included as risk factors in guidelines for minor head injury. This is confirmed in our study.

Patients with LOC or PTA are at higher risk of intracranial complications than patients without LOC and PTA, but the risk in patients without LOC and PTA should not be ignored. In the past, the risk of intracranial complications in patients without LOC or PTA was estimated to be low and a head CT did not seem necessary.[22] This resulted in still widely used guidelines that exclude patients without LOC and PTA for imaging. However, in a few studies, the occurrence of traumatic lesions in patients without LOC and PTA was described and ranged between 2.9–10%.[15,21,23,24] This is similar to our results and confirms our hypothesis that the risk of complications in patients without LOC and PTA is not always negligible. It should be noted that in our study, where centers used the CHIP rule, the majority of patients without LOC and PTA were scanned because they had other risk factors. Only a small portion of the patients without LOC and PTA had no other risk factors.

With the increasing prevalence of patients with minor head injury presenting at the emergency departments, it is important that adequate guidelines are used to help decide if patients need a head CT.[2,25] If guidelines only apply to a subgroup of patients, such as patients with LOC or PTA, clinical management for the patients without LOC and PTA is not clear. This results in practice variation with unnecessary scanning or discharge of patients at risk. Further, clinical management is unclear not only for patients without LOC and PTA, but also for patients with unknown LOC or PTA. After sustaining a head injury, it is not uncommon that patients do not know whether or not they experienced LOC or PTA, especially when there was no relative or witness present. In our study we found that in 8% of the patients LOC and PTA was unknown and that 9% of these patients had a traumatic finding on CT. Patients with unknown LOC and PTA were older and more often intoxicated with alcohol or

drugs, which could lead to performing a CT regardless of presence of any other risk factors.

Two other studies described the proportion of patients with unknown LOC or PTA; 18–32% for LOC and 10–24% for PTA.[7,26] However, in most other studies the proportion of patients with missing or unknown LOC and PTA was never mentioned. Our results suggest that clinical guidelines for minor head injury should not only include LOC and PTA as separate risk factors, but they should also be made applicable to patients without and unknown LOC and PTA. Examples of guidelines that comply with these requisites are the National Institute for Health and Care Excellence (NICE) head injury guideline, the CHIP prediction rule, and the American College of Emergency Physicians (ACEP) guideline for mild traumatic brain injury.[7–9] In the future, clinical guidelines might be improved by incorporating blood-based biomarkers to predict intracranial traumatic findings on CT, although the additional diagnostic value of these biomarkers over clinical characteristics remains to be established.[27,28] For instance, the opportunities for improvement of the CHIP prediction model are reflected by the relatively small R2 values of the full model (< 15%; Fig. 2). Substantial variability may be explained by risk factors that have not (yet) been included in the CHIP prediction model.

An important strength of this study is that all consecutive blunt head injury presenting at the emergency department were included. Studies in minor head injury patients often only include patients with a CT or patients with specific risk factors and a CT, causing the analysis to be limited to a subgroup of all patients with minor head injury presenting at the emergency department. However, this strength is also associated with a limitation of our study, being that the outcome of all patients without a CT (21%) was imputed for the univariable and multivariable analyses. In the participating centers, assessment whether or not patients with minor head injury needed a CT was based on national or local guidelines, and it was not feasible to acquire a CT in all patients for the purpose of this study. Therefore, we collected all possible risk factors and imputed the outcome based on these risk factors and patients with known outcome using multiple imputation. This resulted in an estimate of 18 more patients with a traumatic intracranial finding on CT and no patients with potential neurosurgical lesions. Further, variability in local guideline adherence may have influenced CT use. Unfortunately, information on guideline adherence was not available in our study.

Other limitations should also be acknowledged. For instance, no gold standard for PTA assessment exists and there is controversy about the preferred method to measure the presence and duration of PTA. Most centers in this study assessed PTA by asking the patients a few orientation questions, which could lead to discrepancies of the PTA duration. Additionally, patients undergoing a neurosurgical intervention in a different hospital might have been missed. However, we believe this is unlikely

because the participating centers were all primary neurosurgery centers in the area. Nevertheless, we used potential neurosurgical lesion as a secondary outcome, and those findings were not affected by missing neurosurgical interventions.

To conclude, patients with neither LOC nor PTA are at risk of intracranial complications if other risk factors are present. This risk is low, but a low risk of a potential neurosurgical lesion or neurosurgical intervention is not negligible. Further, identification of intracranial traumatic findings causes a change in management, such as admission to the hospital for observation, temporary stop of oral anticoagulation, and a different follow-up policy. Clinicians should be aware of the risk of intracranial complications in patients without LOC and PTA, and clinical guidelines should include patients without LOC and PTA, such as the NICE head injury guideline, the CHIP rule, and the ACEP mild traumatic brain injury guideline. In addition, we confirmed that LOC and PTA are important risk factors in blunt traumatic head injury and we recommend that guidelines should include LOC and PTA as separate risk factors rather than as diagnostic selection criteria.

References

1. Peeters, W., van den Brande, R., Polinder, S., Brazinova, A., Steyerberg, E.W., Lingsma, H.F. and Maas, A.I. (2015). Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 157, 1683-1696.
2. Maas, A.I.R., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J and Investigators (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 16, 987-1048.
3. Shukla, D. and Devi, B.I. (2010). Mild traumatic brain injuries in adults. J Neurosci Rural Pract 1, 82-88.
4. Kristman, V.L., Borg, J., Godbolt, A.K., Salmi, L.R., Cancelliere, C., Carroll, L.J., Holm, L.W., Nygren-de Boussard, C., Hartvigsen, J., Abara, U., Donovan, J. and Cassidy, J.D. (2014). Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95, S265-277.
5. Carroll, L.J., Cassidy, J.D., Holm, L., Kraus, J., Coronado, V.G. and Injury, W.H.O.C.C.T.F.o.M.T.B. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med, 113-125.
6. Pandor, A., Goodacre, S., Harnan, S., Holmes, M., Pickering, A., Fitzgerald, P., Rees, A. and Stevenson, M. (2011). Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technol Assess 15, 1-202.
7. Smits, M., Dippel, D.W., Steyerberg, E.W., de Haan, G.G., Dekker, H.M., Vos, P.E., Kool, D.R., Nederkoorn, P.J., Hofman, P.A., Twijnstra, A., Tanghe, H.L. and Hunink, M.G. (2007). Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med 146, 397-405.
8. National Clinical Guideline, C. (2014). National Clinical Guidance Centre. (2014). CG 176 Head Injury Triage, assessment, investigation and early management of head injury in children, young people and adults. . National Institute for Health and Care Excellence.
9. Jagoda, A.S., Bazarian, J.J., Bruns, J.J., Jr., Cantrill, S.V., Gean, A.D., Howard, P.K., Ghajar, J., Riggio, S., Wright, D.W., Wears, R.L., Bakshy, A., Burgess, P., Wald, M.M., Whitson, R.R., American College of Emergency, P., Centers for Disease, C. and Prevention (2008). Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. Ann Emerg Med 52, 714-748.
10. Stiell, I.G., Wells, G.A., Vandemheen, K., Clement, C., Lesiuk, H., Laupacis, A., McKnight, R.D., Verbeek, R., Brison, R., Cass, D., Eisenhauer, M.E., Greenberg, G. and Worthington, J. (2001). The Canadian CT Head Rule for patients with minor head injury. Lancet 357, 1391-1396.
11. Haydel, M.J., Preston, C.A., Mills, T.J., Luber, S., Blaudeau, E. and DeBlieux, P.M. (2000). Indications for computed tomography in patients with minor head injury. N Engl J Med 343, 100-105.
12. Unden, J., Ingebrigtsen, T., Romner, B. and Scandinavian Neurotrauma, C. (2013). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 11, 50.
13. Servadei, F., Teasdale, G., Merry, G. and Neurotraumatology Committee of the World Federation of Neurosurgical, S. (2001). Defining acute mild head injury in adults: a proposal based on prognostic factors, diagnosis, and management. J Neurotrauma 18, 657-664.
14. Foks, K.A., Cnossen, M.C., Dippel, D.W.J., Maas, A., Menon, D., van der Naalt, J., Steyerberg, E.W., Lingsma, H. and Polinder, S. (2017). 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. J Neurotrauma. 2017(34):2529-35.
15. Smits, M., Hunink, M.G., Nederkoorn, P.J., Dekker, H.M., Vos, P.E., Kool, D.R., Hofman, P.A., Twijnstra, A., de Haan, G.G., Tanghe, H.L. and Dippel, D.W. (2007). A history of loss of consciousness or post-traumatic amnesia in minor head injury: "conditio sine qua non" or one of the risk factors? J Neurol Neurosurg Psychiatry 78, 1359-1364.
16. Mower, W.R., Gupta, M., Rodriguez, R. and Hendey, G.W. (2017). Validation of the sensitivity of the National Emergency X-Radiography Utilization Study (NEXUS) Head computed tomographic (CT) decision instrument for selective imaging of blunt head injury patients: An observational study. PLoS Med 14, e1002313.
17. Foks, K.A., van den Brand, C.L., Lingsma, H.F., van der Naalt, J., Jacobs, B., de Jong, E., den Boogert, H.F., Sir, O., Patka, P., Polinder, S., Gaakeer, M.I., Schutte, C.E., Jie, K.E., Visee, H.F., Hunink, M.G.M., Reijners, E., Braaksma, M., Schoonman, G.G., Steyerberg, E.W., Jellema, K. and Dippel, D.W.J. (2018). External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands. Bmj 362, k3527.
18. Lingsma, H.F., Roozenbeek, B., Steyerberg, E.W., Murray, G.D. and Maas, A.I. (2010). Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol 9, 543-554.
19. Ono, K., Wada, K., Takahara, T. and Shirotani, T. (2007). Indications for computed tomography in patients with mild head injury. Neurol Med Chir (Tokyo) 47, 291-297; discussion 297-298.
20. Fabbri, A., Servadei, F., Marchesini, G., Dente, M., Iervese, T., Spada, M. and Vandelli, A. (2005). Clinical performance of NICE recommendations versus NCWFNS proposal in patients with mild head injury. J Neurotrauma 22, 1419-1427.
21. Ibanez, J., Arikan, F., Pedraza, S., Sanchez, E., Poca, M.A., Rodriguez, D. and Rubio, E. (2004). Reliability of clinical guidelines in the detection of patients at risk following mild head injury: results of a prospective study. J Neurosurg 100, 825-834.
22. Teasdale, G.M., Murray, G., Anderson, E., Mendelow, A.D., MacMillan, R., Jennett, B. and Brookes, M. (1990). Risks of acute traumatic intracranial haematoma in children and adults: implications for managing head injuries. Bmj 300, 363-367.
23. Sharif-Alhoseini, M., Khodadadi, H., Chardoli, M. and Rahimi-Movaghar, V. (2011). Indications for brain computed tomography scan after minor head injury. J Emerg Trauma Shock 4, 472-476.
24. Sheehan, A. and Batchelor, J.S. (2012). A retrospective cohort study to re-evaluate clinical correlates for intracranial injury in minor head injury. Emerg Med J 29, 899-901.
25. Van den Brand, C.L., Karger, L.B., Nijman, S.T., Hunink, M.G., Patka, P. and Jellema, K. (2017). Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. Eur J Emerg Med.
26. Strand, I.H., Solheim, O., Moen, K.G. and Vik, A. (2012). Evaluation of the Scandinavian guidelines for head injuries based on a consecutive series with computed tomography from a Norwegian university hospital. Scand J Trauma Resusc Emerg Med 20, 62.
27. Bazarian, J.J., Biberthaler, P., Welch, R.D., Lewis, L.M., Barzo, P., Bogner-Flatz, V., Gunnar Brolinson, P., Buki, A., Chen, J.Y., Christenson, R.H., Hack, D., Huff, J.S., Johar, S., Jordan, J.D., Leidel, B.A., Lindner, T., Ludington, E., Okonkwo, D.O., Ornato, J., Peacock, W.F., Schmidt, K., Tyndall, J.A., Vossough, A. and Jagoda, A.S. (2018). Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol 17, 782-789.
28. Maas, A.I.R. and Lingsma, H.F. (2018). ALERT-TBI study on biomarkers for TBI: has science suffered? Lancet Neurol 17, 737-738.

Supplementary Table 1. Overview of CT guidelines used in the participating centers

	National guideline	Local guideline
Number of centers	5	1
1 or more major criteria	- GCS < 15 (including persisting PTA) - 2 or more points deterioration in GCS (1 hour after presentation) - Vomiting - Posttraumatic seizure - Signs of skull fracture - Pedestrian or cyclist versus vehicle - Ejected from motor vehicle - Posttraumatic amnesia ≥ 4 hours - Use of anticoagulants - Focal neurologic deficit - Suspicion of intracranial injury after focal "high impact" injury	- GCS < 15 - 2 or more points deterioration in GCS (1 hour after presentation) - Vomiting - Posttraumatic seizure - Age ≥60 years - Signs of skull fracture - Dangerous mechanism (Pedestrian or cyclist versus vehicle; Ejected from motor vehicle; Fall from more than 1m or 5 stairs; Or equivalent mechanism) - Posttraumatic amnesia ≥ 4 hours - Coagulopathy, e.g. use of coumarin derivate (INR >1.7), NOACs, or chronic alcohol abuse - Focal neurologic deficit - Intoxication that impairs neurological examination
2 or more minor criteria	- Fall from any elevation - Loss of consciousness - Posttraumatic amnesia 2-4 hours - Visible injury to the head, excluding the face (without signs of fracture) - 1 point deterioration in GCS (1 hour post presentation) - Age > 40 years	- Fall from < 1 m - Loss of consciousness - Posttraumatic amnesia 2-4 hours - Persisting posttraumatic amnesia (recall deficit) - Traumatic injury above the clavicles - 1 point deterioration in GCS (1 hour post presentation) - Age 40-60 years

CT = computed tomography, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia

Chapter 8

Update of the CHIP (CT in head Injury Patients) decision rule for patients with minor head injury

Submitted

Crispijn L. van den Brand*
Kelly A. Foks*
Hester F. Lingsma
Joukje van der Naalt
Bram Jacobs
Eline de Jong
Hugo F. den Boogert
Özcan Sir
Peter Patka
Suzanne Polinder
Menno Gaakeer
Charlotte E. Schutte
Kim E. Jie
Huib F. Visee
Myriam G. M. Hunink
Eef Reijners
Meriam Braaksma
Guus Schoonman
Ewout W. Steyerberg
Diederik W.J. Dippel
Korné Jellema

Chapter 9

General Discussion

For patients with minor head injury (MHI) and mild traumatic brain injury (TBI) many controversies exist about diagnostic decisions, admission and discharge policy, and type of care planned at discharge from the emergency department. The optimal acute management at the emergency department remains unclear, despite the high incidence of at least two million patients each year in Europe.[1] In order to optimize management, we need to gain more insight into the current acute management in clinical practice. Because of the high incidence, small improvements in policy could lead to an important cumulative healthcare benefit. The first aim of this thesis was to describe the extent of practice variation in management of patients with MHI or mild TBI at the emergency department. Because the decision of performing a head computed tomography (CT) plays a crucial role in acute management of patients with MHI, the second aim of this thesis was to investigate how CT decision rules for MHI could be improved. This chapter describes the main findings of the papers in this thesis, discusses general limitations, clinical implications and recommendations for future research.

Interpretation of main findings

Practice variation in minor head injury management at the emergency department

To describe the practice variation in management of patients with mild TBI at the emergency department we analysed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study (**chapter 2-3**). The questionnaire results showed large between center variation in acute management of mild TBI at the emergency department in Europe (**chapter 2**). First, we found important variation in definitions of mild TBI; about 60% of the centers defined mild TBI as a Glasgow Coma Scale (GCS) score of 13-15 and 40% as a GCS score of 14-15. Secondly, we found that various guidelines or decision rules for the use of head CT were used and 21% of the centers used no guidelines at all. Besides the fact that we found that guidelines are not used in some centers, in other centers the actual policies diverged from what is recommended in the guidelines they use. In a recent systematic review it was also shown that guideline adherence in TBI is suboptimal.[6] This lack of adherence to guidelines could indicate the need for better evidence and new guidelines. Lastly, we found differences in admission and discharge policies between centers. In the actual CENTER-TBI dataset we also found between center practice variation in admission and discharge decisions (**chapter 3**). Our studies confirm the practice variation in mild TBI management at emergency departments across Europe identified in previous questionnaire studies.[3-5] However, **chapter 3** describes results of the first observational cohort study that studies European center differences for mild TBI management. About 40% of patients with pre-injury anticoagulation use and 12% of patients with traumatic intracranial

findings on CT were discharged home after presentation at the emergency department. 36% patients with a normal head CT were admitted to the hospital. If for example patients with pre-injury anticoagulation use and traumatic intracranial findings are discharged home without treatment this could lead to worse outcomes. And if patients with a normal head CT and no other reason for admission to the hospital are admitted this leads to inefficient costly management of mild TBI.

To analyze if implementing a new CT guideline for MHI leads to practice variation in CT scanning over time, we created a retrospective database by extracting data from electronic health reports from 1997 to 2014, using natural language processing. Over two decades we found that the number of CTs performed for head trauma gradually increased, while the proportion of patients with intracranial traumatic findings decreased (**chapter 4**). In 2011 a new CT guideline based on the CHIP decision rule was implemented, resulting in a significant increase in CT use (82%-88%) and significant decrease in the proportion of patients with intracranial traumatic findings (12%-10%). Despite the increase in CT use after implementation of the new guideline, the guideline did lead to a reduction in CT scanning of 12% in contrast to scanning all patients. Cost-effectiveness studies have shown that scanning all patients with MHI is more cost-effective than missing only a few intracranial traumatic findings requiring neurosurgery due to selective scanning.[7, 8] Thus, if the new CT guideline based on the CHIP decision rule identifies all serious traumatic findings, while reducing CT use by 12%, this would be preferable to scanning all patients and be more cost-effective. Furthermore, the increase in CT use after implementation of the new CT guideline could be explained by a better adherence to the guideline by physicians if the guideline was previously underutilized.

Blunt cerebrovascular injury

In contrast with MHI, limited research is available for identifying patients with blunt cerebrovascular injury after a head or neck trauma. Blunt cerebrovascular injury involves injuries to the vertebral or carotid arteries and could result in serious consequences such as ischemic stroke or death.[9] In our center, often discussions occur about the local guideline. To investigate the practice variation in use of CT angiography (CTA) and treatment, we conducted a retrospective study between 2010 and 2016. In total 41 patients (14%) were diagnosed with blunt cerebrovascular injury (**chapter 5**). Although the frequency of patients with blunt cerebrovascular injury was comparable to previous studies, we were surprised by the relatively high frequency observed in our center.[10, 11] We believed in our center blunt cerebrovascular injury was very scarce and did not expect such a relative high incidence. Interestingly, almost half of the patients (43%) received a CTA not according to the local guideline. The most frequent indication to perform a CTA

outside the local guideline was hanging or strangulation; in these 66 patients, only two patients had blunt cerebrovascular injury. This lack of adherence of the local guideline could be the result of recommendations based on low-level evidence. It indicates the need for a new guideline.

Improving CT decision rules

To investigate how CT decision rules for MHI could be improved, the second aim of this thesis, we used the CHIP Refinement Study (CREST). As described in **chapter 2**, currently many different CT decision rules for MHI are used in Europe. In the Netherlands, the national and local guidelines are based on the CHIP decision rule which was developed in 2007.[12,13] However, an external validation study had not yet been performed. An external validation study is necessary to determine generalizability of the rule in other patient cohorts than the development cohort.[14, 15] In **chapter 6** we described the results of the external validation study where we compared the performance of the CHIP rule with three frequently used rules: the New Orleans Criteria, the Canadian CT Head Rule and the NICE guidelines for head injury. The majority of the patients received a head CT (82%) and in 8% of the patients (intra)cranial traumatic findings were identified. The proportion of patients with intracranial traumatic findings in our study was comparable with other studies.[13, 16, 17] We showed that application of different decision rules led to a variation of unnecessary head CTs and some missed traumatic findings on CT. Previous studies have externally validated the New Orleans Criteria, Canadian CT Head Rule and NICE guideline, and this study adds the CHIP rule to this list and compares it with the other rules.[18-20] Based on the results we recommend to use the CHIP rule, because it missed only a few patients with potential serious lesions and led to a substantial reduction of head CTs.

In frequently used guidelines the policy for patients without loss of consciousness and posttraumatic amnesia is often unclear because only patients with loss of consciousness or posttraumatic amnesia are included.[16, 17, 21] Sometimes the patients without loss of consciousness and posttraumatic amnesia will therefore be discharged home without a head CT. In our CREST dataset we analyzed the presence and absence of loss of consciousness and posttraumatic amnesia on intracranial complications after MHI. In **chapter 7** we showed that a small proportion of patients without loss of consciousness and posttraumatic amnesia had traumatic findings on CT (67/2249). One of these patients even needed a neurosurgical intervention for an epidural hematoma and depressed skull fracture. Only a few other studies describe the occurrence of traumatic findings in patients without loss of consciousness and posttraumatic amnesia was described, however these patients are often not mentioned in studies.[22-24] With our study we confirmed that patients without loss of consciousness and posttraumatic amnesia are at risk of intracranial complications and

should not be excluded from clinical guidelines. Examples of guidelines that include these patients are the CHIP rule and NICE guidelines.

In **chapter 6** we described that the CHIP rule led to a substantial reduction of CT scans but missed a few patients with potential serious lesions. Therefore, we performed an update of the CHIP decision rule in **chapter 8**. The updated CHIP rule consists of 12 significant risk factors: signs of a skull base fracture, GCS score at presentation, contusion of the skull, vomiting (more than once), age, presence of posttraumatic amnesia (or unknown), presence of loss of consciousness (or unknown), neurological deficit, fall from any elevation, use of antiplatelet agents (excluding carbascalaatcalcium monotherapy), high energy trauma, and focal high impact trauma. Compared to the original CHIP rule use of antiplatelets, high energy trauma and focal high impact trauma are added to the rule. Surprisingly, pre-injury use of anticoagulants was not included as a risk factor in this updated version of the CHIP rule. Possibly due to a very high number of patients in the dataset with pre-injury use of anticoagulants and no traumatic findings on CT. In the original CHIP rule use of anticoagulants had an adjusted odds ratio of 2.4.[13] In the current study an adjusted odds ratio of -0.4 was found, resulting that this risk factor could not be included in the updated rule. However, because patients with traumatic intracranial findings and anticoagulants use may have a worse outcome, it was recommended to add use of anticoagulants as a risk factor in clinical guidelines.

General limitations

Chapter 2, which describes results of practice variation in the CENTER-TBI centers is based on two questionnaire surveys. Although in this study consistency checks were used and the 'general policy' was asked rather than individual preferences, in questionnaire studies the results completely depend on the interpretation of the questions by the investigators and their willingness to be truthful. Therefore, the results of this chapter should be interpreted with care.

Due to the study design of CENTER-TBI in which patients were included in three strata (emergency room stratum, admission stratum and intensive care stratum), some participating centers only enrolled patients in one or two strata. Because we wanted to investigate the variation in admission and discharge policies at the emergency department across centers in **chapter 3**, we needed centers that enrolled patients in all three strata. This resulted in exclusion of more than half of the centers and patients for the analysis. Therefore, the described practice variation could be under- or overestimated.

In the retrospective study about practice variation in management of blunt cerebrovascular injury (**chapter 5**) we included only ER patients who had a CTA scan. Because of the high number of patients with any blunt traumatic head or neck injury between 2010 and 2016 it was not feasible to extract information about risk factors and outcome from all patients. However, the incidence of blunt cerebrovascular injury and comparison of odds ratios between different risk factors associated with blunt cerebrovascular injury would have been helpful for the interpretation of the results.

Not all patients in the CREST study (**chapter 6-8**) had a CT scan, because centers adhered to local guidelines. This constitutes a serious limitation, because some patients with no or one risk factor might not have had a CT scan. Therefore, intracranial traumatic findings in these patients could have been missed, resulting in a slight overestimation of the sensitivity and underestimation of the specificity. A possible solution for this problem could have been a follow-up study in these patients without a CT. However, this study was conducted without funding and therefore this was not feasible. In the studies described in **chapter 6-8** we solved this problem by using imputation of the outcome based on their risk factors.[25]

Clinical implications

Practice variation in minor head injury management at the emergency department

With our CENTER-TBI and two retrospective studies (**chapter 2-5**) we confirmed that there is practice variation in the management of MHI and mild TBI at the emergency department. This practice variation could possibly lead to worse patient outcomes if for example patients with pre-injury anticoagulants use and with traumatic findings on CT are discharged home without follow-up. Our analysis is the first step towards more insight in how to improve emergency care and optimize management. In addition, the differences we identified in use of definition for mild TBI, use of CT and CTA guidelines and in admission and discharge policies are especially helpful for policy and guideline makers.

We identified a possible valuable tool to monitor CT use after implementation of a new guideline in **chapter 4**; natural language processing. Natural language processing enabled the extraction of large number of clinical variables from heterogenous electronic health reports.[26, 27] It takes time and many efforts to build the algorithm to extract data, but once the algorithm is built, it can be used as a tool to monitor the use of CT over time. Furthermore, a similar algorithm can be used to monitor not only CT use, but also the use of other diagnostic tests such as CTA in blunt cerebrovascular injury.

Blunt cerebrovascular injury

In our retrospective study we found that almost half of the patients with a CTA scan were not scanned according to the local guideline and in some patients no antithrombotic treatment was considered (**chapter 5**). We believe it is important to identify patients with blunt cerebrovascular injury with CTA, monitor them closely and consider early antithrombotic treatment. This strategy needs testing in a randomized controlled trial. The national guideline should be updated and locally implemented in all departments that are involved in the acute management of patients with possible blunt cerebrovascular injury.

Improving CT decision rules

The most important clinical implication from this thesis is that current clinical guidelines for patients with MHI and mild TBI should be updated. Because of the low risk of intracranial complications not all patients need a head CT and with an increasing incidence of MHI at the emergency department, unnecessary CT scans will lead to overcrowding at the emergency department, increasing costs, CT radiation, and burden for the patient.[28, 29] To prevent or reduce these problems, clinical guidelines based on adequate decision rules are necessary. In our external validation study (**chapter 6**) we found that it is justified to use any of the four studied decision rules; the New Orleans Criteria, the Canadian CT Head Rule, the NICE guidelines for head injury, or the CHIP rule. The preference for a rule depends on how many unnecessary CT scans the physician is willing to make to prevent one missed lesion on CT. The New Orleans Criteria had the highest sensitivity and identified all patients with serious findings, but nearly all patients would need a CT scan. On the other hand, the NICE guidelines had the highest specificity and lowest proportion of patients who needed a CT scan, but many serious findings would be missed. The CHIP rule missed only a few potential serious lesions and led to a substantial reduction of head CTs, and therefore we recommend to use this rule.

We updated the CHIP rule in **chapter 8**, which now consists of 12 risk factors instead of the 15 risk factors in the original CHIP rule. Less risk factors will make it easier to use the rule in clinical practice. Furthermore, it was recommended to add pre-injury use of anticoagulants as an extra risk factor. Based on the results of this study all guidelines based on the original CHIP rule should be updated. For example, in the Netherlands, the national guideline is based on the original CHIP rule and now clearly needs an update.

In **chapter 7** we described that patients without loss of consciousness and posttraumatic amnesia are also at risk of intracranial complications and therefore recommend to use a guideline or decision rule that includes a policy for patients

without loss of consciousness and posttraumatic amnesia. Examples of guidelines that include a policy for patients without these symptoms are the original and updated CHIP decision rule and the NICE guidelines for head injury.

Recommendations for future research

Practice variation in minor head injury management at the emergency department

Definition of mild TBI

Future research should focus on the definition of mild TBI. In **chapter 2** we found that different GCS scores are used for the definition of mild TBI; some centers use a GCS score of 13-15 and other centers use a GCS score of 14-15. In addition, in **chapter 7** we focused on patients without loss of consciousness and posttraumatic amnesia. Patients without these symptoms are often not seen as a patient with mild TBI, because the presence of loss of consciousness or posttraumatic amnesia is often warranted for the definition of mild TBI.[30, 31] Consequently, these patients are not included in frequently used CT decision rules.[16, 17] We showed that patients without loss of consciousness and posttraumatic amnesia have a small risk of intracranial complications and should not be excluded from decision rules. Future research should include patients without loss of consciousness and posttraumatic amnesia and it should be investigated if these patients also have long-term post-traumatic symptoms, because in many studies these patients are not included in the analysis.

Comparative effectiveness research

In **chapter 2 and 3** we showed practice variation in the management of mild TBI across centers. To optimize management for mild TBI, future research is needed to investigate whether the identified practice variation in management across centers is associated with different patient outcomes. A method to explore the effectiveness of different policies is comparative effectiveness research.[32] Comparative effectiveness research compares outcome data from centers that routinely follow a specific policy with centers that do not.[33] Large observational studies are needed because it concerns small risks with very serious consequences. Examples of policies that could be investigated are discharge of patients with anticoagulation use or intracranial traumatic findings, admission of mTBI patients with a normal head CT, admission of mTBI to a high care unit or intensive care unit for neurological observation, and type of care planned at discharge.

Blunt cerebrovascular injury

In **chapter 5** we showed practice variation in management of patients with blunt cerebrovascular injury in our center. The majority of studies in this field have a retrospective study design, as was our study. Because of the serious consequences of

blunt cerebrovascular injuries such as ischemic strokes and death, optimal screening criteria and treatment options should be further investigated in prospective cohort studies. In addition, a randomized controlled trial is necessary to identify the optimal treatment.

Improving CT decision rules

External validation

In **chapter 8** we updated the CHIP decision rule, but this updated rule again needs an external validation study to test if the rule is generalizable and is also applicable in patient cohorts other than the development cohort. To increase generalizability of the updated CHIP rule, validation data should preferably be collected in other countries than the Netherlands or in different settings.

Over time patient populations at emergency departments can change. For example, nowadays we see a higher incidence of falls and older female patients in high income countries. Because of this change in patient populations, it is necessary to continue to conduct external validation studies in the future to assess the clinical performance of the used clinical guidelines and CT decision rules.

Biomarkers

In recent years the use of biomarkers in addition to CT decision rules has shown promising results.[34] An example is the biomarker S100 calcium-binding protein B (S100B).[35] S100B is even incorporated in the Scandinavian guidelines for head injury to help decide if a CT is necessary.[21] In **chapter 2**, we described that six out of 71 centers currently use S100B as a prognostic biomarker, of which three Scandinavian centers. The question remains, as the results are so promising, why are biomarkers currently not used more often. More research is needed that focus on the addition of biomarkers in CT decision rules.

This thesis focused on the improvement of acute management for MHI, but more research is necessary in early recognition and treatment of post-traumatic symptoms. In 15-25% of the patients these problems are long-term and interfere with daily life. In **chapter 2 and 3** I described practice variation in early interventions that could reduce post-traumatic symptoms, but future research should focus on novel treatment options.

Box 1. Recommendations for future research

1. Patients without loss of consciousness and posttraumatic amnesia should be included in studies on mTBI.
2. It should be investigated whether practice variation in management of mild TBI across centers is associated with patient outcome.
3. Optimal screening and treatment options for blunt cerebrovascular injury should be studied in prospective (randomized) studies.
4. The updated CHIP rule should be externally validated to test its generalizability.
5. The addition of information from biomarkers of brain tissue damage to clinical CT decision and prognostic rules should be further studied
6. Early recognition and treatment for post-traumatic symptoms deserves a larger research effort.

Final remarks

In this thesis I have described practice variation in acute management of MHI and mild TBI at the emergency department. To optimize management for mild TBI, future research is needed to investigate whether the identified practice variation across centers is associated with different patient outcomes. Secondly, I investigated how CT decision rules could be improved. I explained how clinical guidelines for MHI patients should be updated and that external validation studies remain necessary in the future to continue to test generalizability of CT decision rules.

References

1. Maas, A.I.R., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J., and Investigators (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 16, 987-1048.
2. Maas, A.I., Menon, D.K., Steyerberg, E.W., Citerio, G., Lecky, F., Manley, G.T., Hill, S., Legrand, V., Sorgner, A., Participants, C.-T. and Investigators (2015). Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 76, 67-80.
3. De Kruijk, J.R., Twijnstra, A., Meerhoff, S. and Leffers, P. (2001). Management of mild traumatic brain injury: lack of consensus in Europe. Brain Inj 15, 117-123.
4. Pulhorn, H., Westmoreland, L. and McMahon, C. (2016). The management of minor head trauma (GCS 15-13) across a Trauma Network. Br J Neurosurg 30, 536-540.
5. Stern, R.A., Seichepine, D., Tschoe, C., Fritts, N.G., Alosco, M.L., Berkowitz, O., Burke, P., Howland, J., Olshaker, J., Cantu, R.C., Baugh, C.M. and Holsapple, J.W. (2016). Concussion Care Practices and Utilization of Evidence-Based Guidelines in the Evaluation and Management of Concussion: A Survey of New England Emergency Departments. J Neurotrauma.
6. Cnossen, M.C., Scholten, A.C., Lingsma, H.F., Synnot, A., Tavender, E., Gantner, D., Lecky, F., Steyerberg, E.W. and Polinder, S. (2016). Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review. J Neurotrauma.
7. Holmes, M.W., Goodacre, S., Stevenson, M.D., Pandor, A. and Pickering, A. (2012). The cost-effectiveness of diagnostic management strategies for adults with minor head injury. Injury 43, 1423-1431.
8. Smits, M., Dippel, D.W., Nederkoorn, P.J., Dekker, H.M., Vos, P.E., Kool, D.R., van Rijssel, D.A., Hofman, P.A., Twijnstra, A., Tanghe, H.L. and Hunink, M.G. (2010). Minor head injury: CT-based strategies for management--a cost-effectiveness analysis. Radiology 254, 532-540.
9. Burlew, C.C. and Biffl, W.L. (2010). Blunt cerebrovascular trauma. Curr Opin Crit Care 16, 587-595.
10. Miller, P.R., Fabian, T.C., Croce, M.A., Cagiannos, C., Williams, J.S., Vang, M., Qaisi, W.G., Felker, R.E. and Timmons, S.D. (2002). Prospective screening for blunt cerebrovascular injuries: analysis of diagnostic modalities and outcomes. Ann Surg 236, 386-393; discussion 393-385.
11. Franz, R.W., Willette, P.A., Wood, M.J., Wright, M.L. and Hartman, J.F. (2012). A systematic review and meta-analysis of diagnostic screening criteria for blunt cerebrovascular injuries. J Am Coll Surg 214, 313-327.
12. de Kruijk, J.R., Nederkoorn, P.J., Reijners, E.P., Hageman, G. and Werkgroep 'Richtlijn voor de opvang en diagnostiek van patienten met licht traumatisch, h.-h. (2012). [Revised practice guideline 'Management of patients with mild traumatic head/brain injury']

1. Herziene richtlijn 'Opvang van patienten met licht traumatisch hoofd-hersenletsel'. Ned Tijdschr Geneeskd 156, A4195.

13. Smits, M., Dippel, D.W., Steyerberg, E.W., de Haan, G.G., Dekker, H.M., Vos, P.E., Kool, D.R., Nederkoorn, P.J., Hofman, P.A., Twijnstra, A., Tanghe, H.L. and Hunink, M.G. (2007). Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: the CHIP prediction rule. Ann Intern Med 146, 397-405.
14. Moons, K.G., Kengne, A.P., Grobbee, D.E., Royston, P., Vergouwe, Y., Altman, D.G. and Woodward, M. (2012). Risk prediction models: II. External validation, model updating, and impact assessment. Heart 98, 691-698.
15. Steyerberg, E.W. and Harrell, F.E., Jr. (2016). Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 69, 245-247.

16. Haydel, M.J., Preston, C.A., Mills, T.J., Luber, S., Blaudeau, E. and DeBlieux, P.M. (2000). Indications for computed tomography in patients with minor head injury. N Engl J Med 343, 100-105.
17. Stiell, I.G., Wells, G.A., Vandemheen, K., Clement, C., Lesiuk, H., Laupacis, A., McKnight, R.D., Verbeek, R., Brison, R., Cass, D., Eisenhauer, M.E., Greenberg, G. and Worthington, J. (2001). The Canadian CT Head Rule for patients with minor head injury. Lancet 357, 1391-1396.
18. Stiell, I.G., Clement, C.M., Rowe, B.H., Schull, M.J., Brison, R., Cass, D., Eisenhauer, M.A., McKnight, R.D., Bandiera, G., Holroyd, B., Lee, J.S., Dreyer, J., Worthington, J.R., Reardon, M., Greenberg, G., Lesiuk, H., MacPhail, I. and Wells, G.A. (2005). Comparison of the Canadian CT Head Rule and the New Orleans Criteria in patients with minor head injury. Jama 294, 1511-1518.
19. Smits, M., Dippel, D.W., de Haan, G.G., Dekker, H.M., Vos, P.E., Kool, D.R., Nederkoorn, P.J., Hofman, P.A., Twijnstra, A., Tanghe, H.L. and Hunink, M.G. (2005). External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. Jama 294, 1519-1525.
20. Bouida, W., Marghli, S., Souissi, S., Ksibi, H., Methammem, M., Haguiga, H., Khedher, S., Boubaker, H., Beltaief, K., Grissa, M.H., Trimech, M.N., Kerkeni, W., Chebili, N., Halila, I., Rejeb, I., Boukef, R., Rekik, N., Bouhaja, B., Letaief, M. and Nouira, S. (2013). Prediction value of the Canadian CT head rule and the New Orleans criteria for positive head CT scan and acute neurosurgical procedures in minor head trauma: a multicenter external validation study. Ann Emerg Med 61, 521-527.
21. Unden, J., Ingebrigtsen, T., Romner, B. and Scandinavian Neurotrauma, C. (2013). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med 11, 50.
22. Smits, M., Hunink, M.G., Nederkoorn, P.J., Dekker, H.M., Vos, P.E., Kool, D.R., Hofman, P.A., Twijnstra, A., de Haan, G.G., Tanghe, H.L. and Dippel, D.W. (2007). A history of loss of consciousness or post-traumatic amnesia in minor head injury: "conditio sine qua non" or one of the risk factors? J Neurol Neurosurg Psychiatry 78, 1359-1364.
23. Ibanez, J., Arikan, F., Pedraza, S., Sanchez, E., Poca, M.A., Rodriguez, D. and Rubio, E. (2004). Reliability of clinical guidelines in the detection of patients at risk following mild head injury: results of a prospective study. J Neurosurg 100, 825-834.
24. Sheehan, A. and Batchelor, J.S. (2012). A retrospective cohort study to re-evaluate clinical correlates for intracranial injury in minor head injury. Emerg Med J 29, 899-901.
25. Sullivan, T.R., Lee, K.J., Ryan, P. and Salter, A.B. (2017). Multiple imputation for handling missing outcome data when estimating the relative risk. BMC Med Res Methodol 17, 134.
26. Kreimeyer, K., Foster, M., Pandey, A., Arya, N., Halford, G., Jones, S.F., Forshee, R., Walderhaug, M. and Botsis, T. (2017). Natural language processing systems for capturing and standardizing unstructured clinical information: A systematic review. J Biomed Inform 73, 14-29.
27. Pons, E., Braun, L.M., Hunink, M.G. and Kors, J.A. (2016). Natural Language Processing in Radiology: A Systematic Review. Radiology 279, 329-343.
28. Van den Brand, C.L., Karger, L.B., Nijman, S.T., Hunink, M.G., Patka, P. and Jellema, K. (2017). Traumatic brain injury in the Netherlands, trends in emergency department visits, hospitalization and mortality between 1998 and 2012. Eur J Emerg Med.
29. Brenner, D.J. and Hall, E.J. (2007). Computed tomography--an increasing source of radiation exposure. N Engl J Med 357, 2277-2284.
30. Kristman, V.L., Borg, J., Godbolt, A.K., Salmi, L.R., Cancelliere, C., Carroll, L.J., Holm, L.W., Nygren-de Boussard, C., Hartvigsen, J., Abara, U., Donovan, J. and Cassidy, J.D. (2014). Methodological issues and research recommendations for prognosis after mild traumatic brain

injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95, S265-277.

31. Carroll, L.J., Cassidy, J.D., Holm, L., Kraus, J., Coronado, V.G. and Injury, W.H.O.C.C.T.F.o.M.T.B. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med, 113-125.
32. Maas, A.I., Menon, D.K., Lingsma, H.F., Pineda, J.A., Sandel, M.E. and Manley, G.T. (2012). Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. J Neurotrauma 29, 32-46.
33. Cnossen, M.C., van Essen, T.A., Ceyisakar, I.E., Polinder, S., Andriessen, T.M., van der Naalt, J., Haitsma, I., Horn, J., Franschman, G., Vos, P.E., Peul, W.C., Menon, D.K., Maas, A.I., Steyerberg, E.W. and Lingsma, H.F. (2018). Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. Clin Epidemiol 10, 841-852.
34. Hansen-Schwartz, J. and Bouchelouche, P.N. (2014). Use of biomarker S100B for traumatic brain damage in the emergency department may change observation strategy. Dan Med J 61, A4894.
35. Calcagnile, O., Unden, L. and Unden, J. (2012). Clinical validation of S100B use in management of mild head injury. BMC Emerg Med 12, 13.

Chapter 10

Summary & Samenvatting

Summary

Minor head injury (MHI) or mild traumatic brain injury (TBI), is a major socioeconomic and health burden throughout the world. MHI has an increasing high incidence and associated acute and long-term complications. However, many controversies exist about the best acute management of patients with MHI and improving the management could improve TBI care and possibly outcomes. Therefore, the overall aim of this thesis is to describe and improve the acute management of MHI.

In the first part of this thesis I investigated the extent of practice variation in acute management of MHI at the emergency department.

In **Chapter 2 and 3**, I presented results from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, a large multicenter prospective cohort study in patients with TBI in Europe. In **Chapter 2**, I described the between center variation in acute management of patients with mTBI at the emergency department in Europe based on questionnaire surveys. There were differences in the definition of mild TBI across centers. Various guidelines and decision rules were used to help physicians decide if a patient needs a head computed tomography (CT) and in some centers no guidelines were used at all. In addition, between center differences in admission and discharge policies were found. In **Chapter 3**, I described the practice variation in management of patients with mTBI after emergency department presentation included in the CENTER-TBI study. There were between center differences in admission and discharge policy of specific subgroups of patients; such as patients with pre-injury anticoagulation use, patients with traumatic intracranial findings on CT and patients with a normal head CT. The practice variation in the acute management of patients with mild TBI that was identified in **Chapter 2 and 3**, provides an opportunity to improve emergency care and optimize management.

In **Chapter 4**, I examined the practice variation of CT use in patients with head trauma over time in one trauma center. In this retrospective study, natural language processing was used to extract data from electronic reports between 1997 and 2014. Over two decades the number of CTs performed for head trauma gradually increased, while the yield (i.e. the proportion of patients with traumatic intracranial findings) decreased. In 2011 a new CT guideline based on the CT in Head Injury Patients (CHIP) rule was implemented, resulting in a significant increase in CT use and significant decrease in yield. Despite the increase in CT use that was found, using a MHI guideline did lead to a “safe” reduction in CT scanning of 12% in contrast to scanning all patients. In addition, natural language

processing could be a valuable tool to monitor CT use after a new guideline has been implemented.

In **Chapter 5**, I described the practice variation of CT angiography (CTA) use and treatment in patients with possible blunt cerebrovascular injury in one trauma center. Between 2010 and 2016, 300 patients received a CTA for screening for blunt cerebrovascular injury and 41 patients (14%) were diagnosed with blunt cerebrovascular injury. Almost half of the patients (43%) received a CTA not according to the local guideline. The most frequent indication to perform a CTA outside the local guideline was hanging or strangulation. In these 66 patients, only two patients suffering from blunt cerebrovascular injury were identified. In more than a third of the patients with blunt cerebrovascular injury treatment was withdrawn (37%) and 16 patients received antithrombotic treatment. Five patients had an in hospital ischemic stroke of which two did receive treatment and three did not. Patients with blunt cerebrovascular injury need to be identified with CTA early, monitored closely and antithrombotic treatment should be considered. More research is needed to investigate the best treatment options for patients with blunt cerebrovascular injury.

CT decision rules and guidelines play a crucial role in the acute management of patients with MHI. Therefore, I focused on how these CT rules for MHI could be improved in the second part of this thesis (**Chapter 6-8**). I used the CHIP Refinement Study (CREST) dataset, a large prospective multicenter cohort study in the Netherlands.

In **Chapter 6**, I described the results of an external validation study of frequently used CT decision rules. The performance of the CHIP rule was compared with three frequently used rules: New Orleans Criteria, Canadian CT Head rule, and National Institute for Health and Care Excellence (NICE) guidelines for head injury. Application of different decision rules led to a variation of some missed traumatic findings and unnecessary head CTs. Because the CHIP rule missed only a few potential serious lesions and led to a substantial reduction of head CTs, it was recommended to use the CHIP rule. In **Chapter 7**, I studied the role of loss of consciousness and posttraumatic amnesia on the risk of intracranial complications in MHI. I showed that a small proportion of patients without loss of consciousness and posttraumatic amnesia had traumatic findings on CT. One patient without loss of consciousness and posttraumatic amnesia underwent a neurosurgical operation. All MHI guidelines should include a policy for patients without loss of consciousness and posttraumatic amnesia, such as the CHIP rule and NICE guidelines. Lastly, in **Chapter 8** we updated the CHIP decision rule. The new rule consists of 12 risk factors: signs of a skullbase fracture, GCS score at presentation, contusion of the

skull, vomiting, age, posttraumatic amnesia, loss of consciousness, neurological deficit, fall from any elevation, use of antiplatelets, high energy trauma, and focal high impact trauma. Based on the results of **Chapter 6-8** clinical guidelines for MHI should be updated and external validation studies remain necessary.

In **chapter 9**, I described the main findings, discussed general limitations, clinical implications and recommendations for further research.

Samenvatting

Licht traumatisch hoofd-hersenletsel (LTH) is een veel voorkomende ziekte en leidt tot wereldwijde sociaaleconomische problemen. De incidentie van LTH blijft stijgen en daarmee ook het aantal patiënten met acute en langdurige complicaties. Er bestaan veel meningsverschillen over de beste acute diagnostiek en behandeling van patiënten met LTH en verbetering hiervan zou de zorg en mogelijk de uitkomsten kunnen verbeteren. Daarom is het doel van dit proefschrift om de acute diagnostiek en behandeling van LTH op de spoedeisende hulp te onderzoeken en te verbeteren.
Samenvatting

In het eerste deel van dit proefschrift heb ik onderzocht of er praktijkvariatie is in de acute diagnostiek en behandeling van LTH op de spoedeisende hulp (**hoofdstuk 2-5**). In **hoofdstuk 2 en 3** liet ik resultaten van de Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) studie zien, een grote prospectieve multicenter cohortstudie bij patiënten met traumatisch hersenletsel in Europa. In **hoofdstuk 2** beschreef ik de variatie op basis van vragenlijstonderzoek tussen ziekenhuizen in het acute management van patiënten met LTH op de spoedeisende hulp in Europa. Ik zag verschillen in het definitie gebruik van LTH in verschillende ziekenhuizen. Daarnaast werden verschillende richtlijnen en beslisregels gebruikt om artsen te helpen beslissen of een patiënt een computed tomography (CT) scan nodig had. In sommige centra werden helemaal geen richtlijnen gebruikt. Ook werden verschillen tussen ziekenhuizen wat betreft opname- en ontslagbeleid beschreven. In **hoofdstuk 3** onderzocht ik de praktijkvariatie in het management van patiënten met LTH op de spoedeisende hulp in de CENTER-TBI dataset. In dit hoofdstuk beschreef ik verschillen tussen ziekenhuizen wat betreft het opname- en ontslagbeleid van specifieke subgroepen van patiënten; zoals patiënten met antistollingsgebruik, patiënten met traumatische intracraniële afwijkingen op CT en patiënten met een normale CT. De praktijkvariatie in het acute management van patiënten met LTH die in **hoofdstuk 2 en 3** werd beschreven, biedt een kans om de zorg op de spoedeisende hulp te verbeteren en LTH management te optimaliseren.

In **hoofdstuk 4** onderzocht ik praktijkvariatie in CT-gebruik bij patiënten met LTH gedurende twee decennia in één traumacentrum. In deze retrospectieve studie werd 'natural language processing' gebruikt om gegevens uit elektronische patiëntendossiers te extraheren. In meer dan twee decennia nam het aantal CT scans dat werd gemaakt voor traumatisch hersenletsel geleidelijk toe, terwijl het percentage patiënten met traumatische intracraniële afwijkingen afnam. In 2011 werd een nieuwe klinische richtlijn geïmplementeerd die was gebaseerd op de CT in Head Injury Patients (CHIP) beslisregel, wat resulteerde in een toename van het CT-

gebruik en een significante daling van het percentage patiënten met traumatische intracraniële afwijkingen. Ondanks de toename in CT-gebruik die werd vastgesteld, leidde het gebruik van de nieuwe richtlijn wel tot een "veilige" reductie van CT scans van 12% ten opzichte van het scannen van alle patiënten met LTH op de spoedeisende hulp. Daarnaast kan 'natural language processing' een waardevol hulpmiddel zijn om CT-gebruik te vervolgen nadat een nieuwe klinische richtlijn is geïmplementeerd.

In **hoofdstuk 5** beschreef ik de praktijkvariatie in diagnostiek en behandeling bij patiënten met mogelijk traumatisch cerebrovasculair letsel in één traumacentrum. Tussen 2010 en 2016 kregen 300 patiënten een CT angiografie (CTA) voor screening en 41 patiënten (14%) werden gediagnosticeerd met traumatisch cerebrovasculair letsel. Bijna de helft van de patiënten (43%) ontving een CTA niet volgens de lokale richtlijn. De meest voorkomende indicatie voor het uitvoeren van een CTA buiten de lokale richtlijn was verhanging of wurging. Van de 66 patiënten met verhanging of wurging hadden slechts twee patiënten traumatisch cerebrovasculair letsel. Bij meer dan een derde van de patiënten met traumatische cerebrovasculaire letsels werd de behandeling stopgezet (37%) en 16 patiënten kregen een antitrombotische behandeling. Vijf patiënten hadden een ischemische beroerte in het ziekenhuis, waarvan er twee antitrombotische behandeling kregen en drie niet. Het is belangrijk om patiënten met traumatisch cerebrovasculair letsel vroeg te identificeren met CTA en antitrombotische behandeling moet worden overwogen. Echter in de toekomst is meer onderzoek naar de behandeling bij patiënten met traumatisch cerebrovasculair letsel nodig.

CT beslisregels en klinische richtlijnen spelen een cruciale rol in de acute diagnostiek van patiënten met LTH. Daarom onderzocht ik in het tweede deel van dit proefschrift (**hoofdstuk 6-8**) hoe de CT beslisregels voor LTH kunnen worden verbeterd. Hiervoor heb ik de CHIP Refinement Study (CREST) dataset gebruikt, een grote prospectieve multicenter cohortstudie in Nederland.

In **hoofdstuk 6** beschreef ik de resultaten van een externe validatie studie van veelgebruikte CT beslisregels. De uitvoering van de CHIP beslisregel werd vergeleken met drie veel gebruikte regels: de New Orleans Criteria, de Canadian CT Head rule, en de National Institute for Health and Care Excellence richtlijnen voor traumatisch hersenletsel. De toepassing van verschillende beslisregels leidde tot een variatie in gemiste traumatische afwijkingen en het maken van onnodige CT scans. Omdat de CHIP beslisregel slechts enkele patiënten met potentiële ernstige laesies miste en leidde tot een aanzienlijke reductie van CT scans, werd het aanbevolen om de CHIP-regel te gebruiken en een update van de CHIP beslisregel uit te voeren. In **hoofdstuk 7** onderzocht ik de rol van bewustzijnsverlies en posttraumatische amnesie op het risico van acute complicaties bij LTH. Ik liet zien dat een klein aantal patiënten zonder bewustzijnsverlies en posttraumatische amnesie wel traumatische

afwijkingen op CT had. En één patiënt zonder bewustzijnsverlies en posttraumatische amnesie onderging zelfs een neurochirurgische operatie. Alle klinische richtlijnen voor patiënten met LTH moeten een beleid hebben voor patiënten zonder bewustzijnsverlies en posttraumatische amnesie, zoals de CHIP beslisregel en National Institute for Health and Care Excellence richtlijn. Ten slotte heb ik in **hoofdstuk 8** de CHIP beslisregel aangepast. De nieuwe beslisregel bestaat uit 12 risicofactoren: tekenen van een schedelbasisfractuur, Glasgow Coma Scale score bij presentatie, contusie van de schedel, overgeven (meer dan een keer), leeftijd, amnesie, bewustzijnsverlies, neurologische uitval, val vanaf elke hoogte, gebruik van trombocyten aggregratieremmers (met uitzondering van carbasalaatcalcium monotherapie), hoog energetisch trauma en focaal hoog impact trauma. Gebaseerd op de resultaten van **hoofdstuk 6-8** moeten de klinische richtlijnen voor patiënten met LTH worden aangepast en zal in de toekomst een nieuwe externe validatie studie nodig zijn.

In **hoofdstuk 9**, heb ik de belangrijkste bevindingen, algemene limitaties, klinische implicaties en aanbevelingen voor onderzoek in de toekomst beschreven.

Chapter 11

Dankwoord
List of publications
PhD portfolio
About the author

Dankwoord

Ik wil een aantal mensen in het bijzonder bedanken voor hun bijdrage aan dit proefschrift.

Allereerst Diederik Dippel, bijna vijf jaar geleden heb jij mij gevraagd om bij jou onderzoek te komen doen naar traumatisch hersenletsel. In eerste instantie was ik verbaasd want wij kennen jou allemaal als de vasculaire neuroloog. Maar je vertelde toen vol enthousiasme dat jij in het verleden ook onderzoek had gedaan naar een predictieregel bij licht schedelhersenletsel en dat daar een vervolgonderzoek voor nodig was. Vooral de eerste jaren waren aardig pittig met alle weekenden includeren en heel veel data invoer, maar ik wil je bedanken voor de kans die je me hebt gegeven. Ik had me geen betere promotor kunnen wensen want je hebt altijd voor mij klaar gestaan en mij met alle hoofdstukken goed geholpen. Ik wil je heel erg bedanken voor al je enthousiasme, kennis, tijd en energie.

Natuurlijk had ik niet een promotor, maar twee! Ewout Steyerberg, ook jou wil ik bedanken. Dankzij jou en Diederik kon ik bij CENTER-TBI aan de slag als klinisch onderzoeker en daarnaast mijn eigen studie opzetten. Helaas vertrok je na mijn eerste jaar vanuit het Erasmus MC naar het LUMC waardoor we elkaar niet altijd hebben gezien. Met name bij het hoofdstuk waar ik zelf het meest trots op ben heb jij enorm geholpen en daar wil ik je voor bedanken.

Naast twee promotoren had ik ook twee co-promotoren, Suzanne Polinder en Hester Lingsma. Jullie wil ik natuurlijk ook heel erg bedanken voor de begeleiding tijdens mijn promotieonderzoek. Hester jij meer inhoudelijk over externe validatie en Suzanne bij jou kon ik terecht met al mijn vragen. Bedankt voor de leuke tijd bij de Maatschappelijke Gezondheidszorg, ik heb veel geleerd!

Ik wil iedereen bedanken die heeft meegewerkt aan het CREST onderzoek. Allereerst Crispijn van den Brand en Korne Jellema. Vier jaar geleden bleek dat we zowel in Rotterdam als in Den Haag dezelfde ambitie hadden om de CHIP beslisregel te gaan valideren. Ik denk dat het de beste beslissing is geweest om dit samen uit te voeren, daardoor hebben we een heel mooi onderzoek neergezet waaruit we goede publicaties kunnen halen. De samenwerking was altijd prettig! Daarnaast wil ik ook alle artsen van de andere ziekenhuizen bedanken voor het meewerken aan ons onderzoek en het invoeren van alle data: Joukje, Bram, Hugo, Ozcan, Peter, Menno, Charlotte, Kim, Huib, Eef, Meriam en Guus, bedankt!

Victor, Iain, Matthieu, Erwin, Ditty en Patricia. In het eerste jaar van mijn promotieonderzoek kwamen we geregeld samen om de patiënten inclusies voor de CENTER-TBI studie te bespreken. En dat was succesvol want Victor en ik hebben hard ons best gedaan om een mooi aantal patiënten te includeren in Rotterdam. Wel jammer dat we daardoor ook zo extreem veel data moesten invoeren, maar het is gelukt! Daarnaast wil ik ook alle andere promovendi van de CENTER-TBI groep van Rotterdam bedanken.

Boudewijn jij was mijn eerste student die ik heb mogen begeleiden, we hebben een mooi onderzoek neergezet samen met Ad, Aad, Iain en Diederik. Bedankt voor alle hulp aan dit hoofdstuk en ik hoop dit onderzoek binnenkort te publiceren.

Alle arts-assistenten neurologie en neurologen. Ik ben nu alweer een tijdje terug in de kliniek en jullie hebben veel geklaag van mij moeten aanhoren over Hora Finita en de laatste loodjes van het promoveren. Gelukkig is het nu zover, mijn boekje is af! Ik ben erg blij om samen met jullie in de kliniek te werken en ik zal mijn kennis van mijn onderzoeksjaren zeker mee nemen.

Lieve familie en vrienden, ik ga jullie niet allemaal bij naam noemen, maar ik wil jullie bedanken voor alle steun tijdens mijn promotieonderzoek. Een uitzondering maak ik op Maaike, Vicky en Simone, mijn kamergenootjes van NA2424. Met jullie heb ik de afgelopen jaren lief en leed gedeeld. Wat was het gezellig in kamer 2424, op congressen, onze trip naar NYC en alle extra uitjes en etentjes. Wat hebben we elkaar ook altijd gemotiveerd om door te werken en door te gaan. Mede dankzij jullie heb ik het voor elkaar gekregen om mijn proefschrift af te krijgen en ben ik nu klaar voor de grote dag. Daarom ben ik blij dat twee van jullie als paranimf achter mij staan, en Simone je weet het, jij bent gewoon mijn derde paranimf! Tot slot lieve papa, mama en Amanda. De afgelopen jaren stonden jullie altijd voor me klaar en kon ik altijd op jullie rekenen. Bedankt voor alle steun.

List of publications

Foks KA, Volovici V, Kwee LE, Haitsma IK, Dippel DW.
Ernstige late intracraniële afwijkingen na licht schedelhersenletsel bij orale anticoagulantia gebruik.
NTVG, 2016

Foks KA, Cnossen MC, Dippel DWJ, Maas A, Menon D, van der Naalt J, Steyerberg EW, Lingsma HF, Polinder S, CENTER-TBI investigators and participants
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

Foks KA, Dijkland SA, Steyerberg EW.
Response to Walker et al. Predicting Long-Term Global Outcome after Traumatic Brain Injury: Development of a Practical Prognostic Tool Using the Traumatic Brain Injury Model Systems National Database.
Journal of Neurotrauma, 2018

Foks KA*, van den Brand CL*, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, den Boogert HF, Sir O, Patka P, Polinder S, Gaakeer M, Schutte CE, Jie KE, Visee HF, Hunink MGM, Reijners E, Braaksma M, Schoonman G, Steyerberg EW, Jellema K, Dippel DWJ.
External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands.
BMJ, 2018

Foks KA*, Pons E*, Dippel DWJ, Hunink MGM.
Impact of guidelines for the management of minor head injury on the utilization and diagnostic yield of CT over two decades, using natural language processing in a large dataset.
European Radiology, 2019

van den Brand CL, **Foks KA**, Jellema K, Dippel DWJ.
Response to 'Intracranial bleeding risk after minor traumatic brain injury in patients on antithrombotic drugs'.
Thrombosis Research, 2019

Foks KA, Dijkland SA, Lingsma HF, Polinder S, van den Brand CL, Jellema K, Jacobs B, van der Naalt J, Sir O, Jie KE, Schoonman GG, Hunink MGM, Steyerberg EW, Dippel DWJ and collaborators.
Risk of intracranial complications in minor head injury: the role of loss of consciousness and posttraumatic amnesia in a multicenter observational study.
Journal of Neurotrauma, 2019

Dijkland SA, **Foks KA**, Polinder S, Dippel DWJ, Maas A, Lingsma HF, Steyerberg EW.
Prognosis in Moderate and Severe Traumatic Brain Injury: A Systematic Review of Contemporary Models and Validation Studies.
Journal of Neurotrauma, 2019

Smit L, **Foks KA**, Hofmeijer J, van der Jagt M.
Sudden unresponsive patient with normal vital signs: what is going on?
Current Opinion Critical Care, 2019

Foks KA, Jellema K, Dippel DWJ.
Diagnostiek bij patiënten met licht traumatisch hoofdletsel: de huidige praktijk.
NTVG, 2019

Portfolio PhD

Name PhD student: Kelly A. Foks
Erasmus MC department: Neurology and Public Health
PhD period: 2015-2019
Promotors: Prof. dr. D.W.J. Dippel and Prof. dr. E.W. Steyerberg
Copromotors: Dr. S. Polinder and Dr. H.F. Lingsma

	Year	Workload (ECTS)
Courses		
BROK (Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers)	2015	1.4
Introduction to systematic reviews – A. Synnot	2015	0.9
Openclinica Introduction training	2015	0.3
Practical Neuroanatomy and Neuroradiology	2015	0.6
Diagnostic research – M.G.M. Hunink	2016	0.7
Biostatistics for clinicians – A. Alonso	2016	0.7
Conceptual foundation of epidemiologic study design – K.J. Rothman	2016	0.7
Practice of epidemiologic analysis – M.A. Ikram and M.W. Vernooij	2016	0.7
Markers and prediction research – J.P.A. Ioannidis	2016	0.7
Scientific Integrity – I.D. de Beaufort	2016	0.3
Advanced systematic review course – E. Donoghue	2017	0.9
Advanced analysis of Prognosis studies – E.W. Steyerberg	2017	0.9
CPO Patient Oriented Research: design, conduct and analysis	2017	0.3
Biomedical English writing and communication – J. Burrough	2017	3.0
Meetings/Seminars		
Weekly seminars Neurology department	2015-2019	2.0
Weekly seminars Public Health department	2016-2019	2.0
Research meetings medical decision making	2017-2019	2.0
Neurotrauma meetings the Netherlands, Utrecht	2015-2019	1.0
Investigator training meeting CENTER-TBI	2015	0.6
Symposium 'Quantative methods for medical research'	2015	0.1
Investigator training meeting CENTER-TBI	2016	0.6
Hands-on datacuration workshop CENTER-TBI	2017	0.7
General Assembly meeting CENTER-TBI	2019	0.6
Teaching activities		
Community Project Public Health	2016-2018	2.1
Supervising Neurology Master's thesis	2017	3.0
Presentations at national and international meetings and conferences		
Oral presentation neurology seminar, Rotterdam: introducing CENTER-TBI and CREST study	2015	0.3
Oral presentation at Emergency Department seminar, Rotterdam: introducing CENTER-TBI and CREST study	2015	1.0
Oral presentation at National Trauma Meeting Netherlands, Utrecht: introducing CREST study	2015	0.3
International Brain Injury Association, eleventh world congress, the Hague – oral presentation	2016	1.0

Oral presentation neurology seminar, Rotterdam: diagnostic and policy in mild traumatic brain injury	2016	1.0
Third congress of the European Academy of Neurology, Amsterdam – oral presentation	2017	1.0
Society for Medical Decision Making (SMDM), Pittsburgh – oral presentation	2017	1.0
Wetenschapsdagen Nederlandse Vereniging voor Neurologie, Nunspeet – oral presentation	2017	1.0
Imaging Research on the Move meeting, Rotterdam - poster	2017	1.0
Oral presentation at Public health research meeting, Rotterdam: External validation of CT decision rules in minor head injury	2018	1.0
Regionale neurologen bijeenkomst Rotterdam, Rotterdam – oral presentation	2019	1.0
Oral presentation neurology seminar, Rotterdam: CTA use and blunt cerebrovascular injury	2019	1.0
Symposium werkgroep Acute Neurology (Nederlandse Vereniging voor Neurologie), Leiden – oral presentation	2019	1.0
National and international conferences		
International Brain Injury Association, eleventh world congress, the Hague	2016	1.2
Third congress of the European Academy of Neurology, Amsterdam	2017	0.7
Society for Medical Decision Making (SMDM), Pittsburgh	2017	1.5
Wetenschapsdagen Nederlandse Vereniging voor Neurologie, Nunspeet	2017	0.7
European Society for Medical Decision Making (ESMDM) conference, Leiden	2018	1.0
Total		42.5

About the author

Kelly Alexandra Foks was born December 25th, 1987 in Voorburg, the Netherlands. After graduating from secondary school 'Sint Maartenscollege' in Voorburg she started studying medicine at the Leiden University in Leiden. At the end of 2012 she obtained her medical degree and started working as a resident neurology at the Alrijne hospital in Leiderdorp in 2013.

In 2014 she started to work as a resident neurology at the Erasmus University Medical Center in Rotterdam and in 2015 she started her training as a neurologist (head prof. dr. P.A.E. Sillevis Smitt). In 2015 she started her PhD project at the Department of Neurology and the Department of Public Health under supervision of prof. dr. D.W.J. Dippel and prof. dr. E.W. Steyerberg, which resulted in this thesis. She designed and coordinated the CHIP Refinement Study (CREST), a multicenter study in patients with minor head injury in the Netherlands. She also executed the participation of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study for the Erasmus University Medical Center.

As of March 2019, Kelly is continuing her training as a neurologist at the Department of Neurology of the Erasmus University Medical Center in Rotterdam.