Guidelines for the Emergency Department management of Traumatic Brain Injury: an Impact Assessment and development of a Prognostic Model to Inform Hospital Admission Decisions

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Abstract

Background

1.4 million patients attend English and Welsh Emergency Departments (ED) annually following head injury. 95% attend with a high level of consciousness, of whom 1% have life-threatening traumatic brain injuries (TBI), whilst 7% have TBI on CT imaging.

National guidelines were introduced in England and Scotland to improve TBI outcomes and reduce hospital admissions. The impact of these guidelines has not been rigorously assessed. They recommend patients with injuries on CT imaging be admitted to hospital in case they deteriorate. Accurate prediction of deterioration could identify patients safe for discharge from the ED.

Aims

Assess the impact of national guidelines on deaths and admissions.
Develop a prediction model for deterioration in patients with injuries identified by CT imaging.

Methods

Interrupted time series analyses using national data for England and Scotland were conducted to evaluate guideline impact.

A systematic review was completed to identify candidate prognostic factors for deterioration. Multivariable logistic regression was used to develop prognostic models using these factors in an English multi-centre retrospective cohort of patients.

Results

Guideline impact varied by age group. Associated reductions in hospital admissions and mortality were found in those aged 16-64. In older patients, an increase in TBI mortality was observed, which was unaffected by guideline introduction.

A prognostic model and decision rule was developed, using data from a cohort of 1699 patients. It achieved a sensitivity of 99.5% (95% CI: 98.1% to 99.9%) and specificity of 7.4% (95% CI: 6% to 9.1%) to a measure of deterioration encompassing need for admission.

Conclusion

This first national evaluation of head injury guidelines to use quasi-experimental methods suggests guideline impact varied by age. This first empirically derived prediction model to inform admission decisions suggests a small proportion of patients could be safely discharged from the ED. External validation is required before clinical use.

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Author's Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Chapter 1: Introduction

Background

Emergency Department classification and management of head injury and traumatic brain injury

In 2014 it was estimated that there were 1.4 million annual attendances to Emergency Departments in England and Wales following head injury (Fig. 1.1).[1] Head injury is defined as any trauma to the head excluding superficial injuries to the face.[1] Research conducted as part of this thesis, found that in 2016 there were around 75,000 hospital admissions for traumatic brain injury (TBI) in adults.[2] TBI is defined as any alteration in brain function or evidence of brain pathology occurring as a result of an external force.[3]

Early specialist intervention can be life-saving.[4] Neurosurgery in patients with severe TBI, can decompress and treat expanding bleeds and other injuries exerting pressure on the brain. Only around 3% of all patients attending the ED following head injury, however, require life-saving specialist care.[3]

The clinical challenge in Emergency Department management of patients with head injury is to ensure that the small number of patients with life-threatening injuries are identified and managed appropriately. The health service challenge is to ensure that we can reduce to a minimum the cost of over-investigating and unnecessarily treating the majority of patients with TBI who can be safely discharged. There is a trade-off between trying to avoid discharging patients who may deteriorate and require intervention and trying to reduce admissions for those who are unlikely to deteriorate.

The Glasgow Coma Scale has been used since 1974 to risk stratify patients presenting with head injury.[5] This is a measure level of consciousness which assesses motor, verbal and eye response to stimulus. The scale scores from 3 to 15, with a lower score indicating

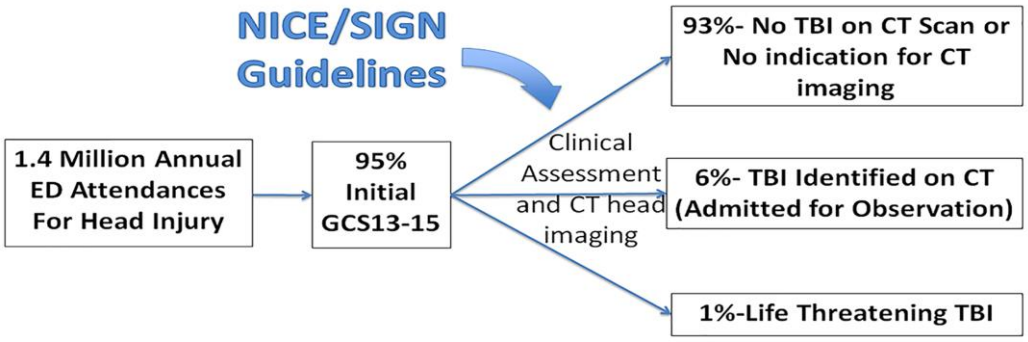
a lower level of consciousness and score of 15 indicating full alertness and orientation (Table 1.1).

Table 1.1: Glasgow Coma Scale[6]

Eyes	Open To voice To pain None	4 3 2 1
Voice	Oriented Confused Inappropriate Incomprehensible None	5 4 3 2 1
Motor	Obeys Commands Localises to pain Withdraws from pain Flexion to pain Extension to pain None	6 5 4 3 2 1

On the basis of an initial GCS score, head injury patients are divided into 3 categories of severity which correspond to different levels of risk of serious TBI and death.[6]
Patients with a GCS ≤8 are classified as having a severe head injury and likely to have life-threatening TBI, with an early mortality rate of 20% reported in this group in 2006.[7] Those with GCS 9-12 are defined as having moderate injuries. Patients with a GCS of 13-15 and are defined as having a minor head injury and mild TBI if there is evidence of altered brain function or brain injury.[1] On presentation to the Emergency Department other causes of depressed level of consciousness need to be considered such as intoxication, extracranial injuries causing shock or hypoxia, or acute and chronic illnesses causing falls in older people.

Figure 1.1: The Emergency Department assessment of head injury



The majority of deaths from TBI and neurosurgical procedures occur in patients in the severe and moderate categories and patients with such low levels of consciousness cannot be considered for discharge from the ED.[1, 8] Ninety-five percent of head injured patients who present to the ED have an initial GCS of 13-15 (Figure 1.1).[1] In this group around 1% patients have life-threatening TBI.[9] This is therefore the most challenging group to balance the identification of significant brain injuries against unnecessary investigation and hospital admission. Computed tomography (CT) head imaging is the clinical gold standard for identifying and ruling out life-threatening TBI requiring neurosurgical intervention in all categories of head injury.[1] As outlined later, in conscious patients CT findings are also used to help determine which patients require inpatient admission from the ED.

The role of national head injury guidelines

Since 2000 a series of national head injury guidelines have been implemented in Scotland and England with the aim of improving the risk assessment of head injured patients in the ED and subsequent management of diagnosed TBI (Figure 1.2). Scottish Intercollegiate Guidelines Network (SIGN) were introduced in 2000 and revised in 2009.[10, 11] National Institute for Health and Care Excellence (NICE) head injury guidelines were introduced in England in 2003 and updated in 2007 and 2014.[1, 12, 13]

The recommendations made by these guidelines are summarised in full in Appendices 1 and 2. In summary, all SIGN and NICE head injury guidelines encouraged increased CT

imaging in patients presenting to the ED with head injury and included recommendations for the clinical management of TBI identified on CT brain scan. The key features of these guidelines are outlined in Table 1.2.

Figure 1.2: Introduction of the NICE and SIGN head injury guidelines

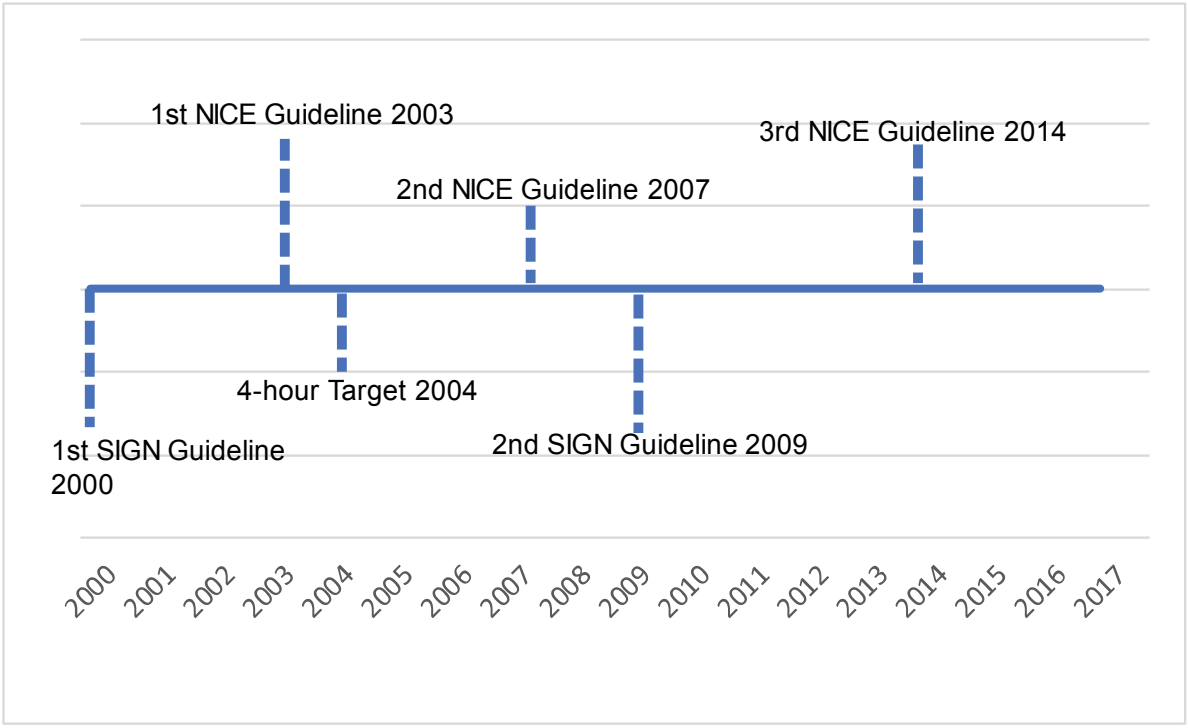


Table 1.2: Key feature of the NICE and SIGN head injury guidelines

Guideline	**Time of introduction**	**Key Features**
1st SIGN Head Injury Guideline	August 2000	Increased indications for CT Imaging Skull x-ray still primary imaging in some patients
1st NICE Head Injury Guideline	June 2003	Implemented the Canadian CT head rule No role for skull x-ray
2nd NICE Head Injury Guideline	September 2007	Recommended management of all patients with severe TBI in specialist centres Specific Paediatric Guidelines Immediate CT imaging all high risk patients
2nd SIGN Head Injury Guideline	May 2009	Amalgam of NICE head injury guideline recommendations for CT imaging No role for skull x-ray Specific Paediatric Guidelines
3rd NICE Head Injury Guideline	January 2014	Recommended CT imaging of all head injured patients taking warfarin, reduction in indications for CT in children

Using research aimed at identifying which conscious head injured patients are at significantly raised risk of life-threatening TBI, the SIGN and NICE guidelines recommended increased CT imaging of initial GCS13-15 head injured patients over successive iterations. They were informed by decision rule research, particularly the Canadian CT Head Rule (CCHR)[9] for adults and Children's Head injury Algorithm for the prediction of Important Clinical Events (CHALICE rule).[14] The guidelines stated which head injured patients needed immediate CT imaging due to high risk of life-threatening injuries; an intermediate risk group who required CT brain scan within 8 hours of head injury, and low risk head injury patients who – if otherwise well - could be safely immediately discharged from the ED.

The introduction of the 1st NICE head injury guideline in 2003 was associated with 2 to 4 fold increase in CT imaging of head injured patients.[15] The increased cost of more CT imaging was forecast to be offset by a reduction in hospital admissions and earlier detection of life-threatening TBI, leading to a reduction morbidity and mortality. Restricted availability of CT imaging before the guidelines were published meant that conscious patients with minor head injury where there was clinical concern of significant TBI were admitted for observation – only receiving CT if their level of consciousness deteriorated. Implementation studies indicated the majority of these patients would be discharged from the ED following normal CT imaging and on this basis economic evaluation models found the NICE head injury guidelines to be cost effective.[15-17]

However, following the introduction of the 1st NICE head injury guideline in 2003, annual hospital admissions for head injury actually increased in England.[18] This may have been the result of detection of brain injuries previously not identified, some without clinical significance, due to increased imaging. However, it was also possible that it reflected the distorting effect of the 4-hour ED target (Figure 1.2 and Table 1.3) that was introduced across the UK in 2004.[19] In Scotland the 4-hour ED target and equivalent SIGN head injury guidelines were introduced at different times (Figure 1.2). This provides the opportunity to explore the independent impact of the guideline introduction and the 4-hour target. The introduction of the 4 hour target essentially means that mild head injury patients who were conscious but where NICE guidance recommended CT within 8 hours of injury

(medium rather than high risk for life threatening TBI) would need to be admitted to hospital pending CT scan if it could not be completed and reported within the 4 hour target time frame. Evaluation of the impact of these health policies on hospital admissions for head injury in Scotland has not previously been undertaken.

Table 1.3: The 4-hour ED target[20]

4-Hour ED performance target	2004	98% of patients attending the ED to be assessed, treated and either discharged or admitted to hospital within 4 hours of arrival. Financial incentives associated with meeting the target.

Research using UK Trauma Audit and Research Network (TARN) registry data presented evidence in 2005 that patients with severe TBI[i] had a reduced risk-adjusted mortality if they were cared for in tertiary specialist centres[ii] where neurosurgical and specialist intensive care services are located.[21] On this basis, the 2007 NICE head injury guideline specifically recommended that all patients with severe TBI be managed in specialist tertiary centres. At the time that the 2007 guideline was introduced concerns were raised about the capacity of specialist tertiary centres in England to meet increased service demand this recommendation would generate.[22] Further research using TARN data found the risk adjusted mortality rate of TBI patients fell in the period 2004 to 2009, and particularly after 2007, when there was an increase in the proportion of TBI patients being managed in specialist centres.[23] There is no equivalent analysis of national trauma registry data in Scotland, and TARN data is collected only on patients who meet specific inclusion criteria and, until 2012, TARN data were collected at only around 50% of hospitals in England. Robust evaluation of the impact of either the NICE or SIGN head injury guidelines on TBI mortality using complete national data has not previously been conducted.

[i] Severe TBI: injuries identified on CT imaging and in patients with an initial GCS ≤8

[ii] Sometimes referred to as specialist neuroscience centres

The NICE and SIGN guidelines aimed to reduce mortality from TBI initially by improving early diagnosis and management of life-threatening TBI through greater access to CT imaging and later through more patients being managed in specialist centres. There is limited evidence that either of these desired outcomes have occurred.

The costs of increased CT imaging associated with the implementation of the SIGN and NICE head injury guidelines were planned to be offset by a reduction in hospital admissions. The limited evidence suggests that in the period following guideline introduction, hospital admissions for head injury actually increased in England. One possible explanation is poor implementation of the guidelines, however, a recent systematic review of head injury guideline adherence found UK NICE guidelines to be the most adhered to internationally. Reported adherence to CT recommendations range between 70% and 100% (mean 87%).[24] In 2005, adherence to SIGN guideline CT imaging indications was reported as 64% at a single centre.[25]

The first part of this thesis presents research that robustly assesses whether the NICE and SIGN head injury guidelines achieved their aims of improving TBI outcomes and reducing hospital admissions. The different timing of guideline implementation in Scotland and England allows the effect of the 4-hour target on hospital admissions to be independently assessed.

An area where both the NICE and SIGN head injury guidelines are unclear is the optimum management of GCS13-15 patients with TBI identified by CT imaging. These patients have a high level of consciousness and are categorised as having mild TBI (mTBI) and have around a 3.5% risk of requiring neurosurgical intervention for their injuries.[26 27, 28] There is no consensus on their management. Some advocate routine repeat CT imaging and admission of all mTBI patients with injuries identified by CT imaging to higher dependency areas due to their risk of serious adverse outcomes.[29] Others argue that selected low risk patients in this group can be safely discharged from the ED. A consensus-derived risk stratification tool (the BIG criteria) is used in some centres in the USA to discharge selected patients.[30, 31] The NICE head injury guidelines, on the other hand, recommend that patients with significant brain injuries identified by CT are admitted to hospital for

observation.[1] However, these guidelines do not define which injuries are significant. It has been argued, that increased CT imaging of minor head injured patients, due to implementation of the NICE guidelines, combined with improved CT imaging has led to more injuries of uncertain significance being identified, contributing to increases in hospital admissions which may not be necessary.[18]

The NICE head injury guidelines are also unclear about which mTBI patients with injuries identified by CT imaging are of sufficiently high risk of deterioration that they may benefit from management by a specialist neurosurgical team. The guidelines state that patients with "new, surgically significant abnormalities on imaging" should be discussed with neurosurgical specialists but do not define such abnormalities.[1] In practice in England, all mTBI patients with injuries identified by CT imaging are currently admitted to hospital for observation but admission is under a range of clinical specialties determined by regional availability of specialist services.[32] In contrast to the clear evidence-based recommended standards for CT imaging and management of severely injured patients, national head injury guidelines recommendations for the management of mTBI patients with injuries on CT are not clear and this has led to variations in care pathways. This in part, reflects the lack of robust evidence to risk stratify this population and inform management recommendations.[28]

The second part of this thesis, presents research to derive a statistical model which accurately predicts the risk of clinical deterioration in mTBI patients with injuries on CT. Accurate risk prediction could be used to help inform hospital admission and specialist referral decisions, so reducing hospital admissions, whilst ensuring those at high risk are referred to specialist neurosurgical facilities.

Research Questions and Aims

Given the limited evaluation of the impact of the NICE and SIGN head injury guidelines and the lack of available evidence to inform the management of mTBI patients with abnormal CT imaging this thesis attempts to answer two research questions.

1) What impact have national head injury guidelines in Scotland and England had on TBI hospital admission and mortality rates?

2) Is it possible to develop a prognostic model for GCS13-15 TBI patients which can identify patients who can be safely discharged from the ED?

These research questions were addressed by the following aims:

1. Assess the impact of national head injury guidelines on:
    - Population based inpatient traumatic brain injury mortality rates
    - Population based admission rates for head injury and traumatic brain injury

2. Develop a prognostic model to accurately predict risk of deterioration in alert patients, with traumatic abnormalities on CT head scan, which could be used to refine the guidelines.

The two are linked in that the second aim could improve the impact of future head injury guidelines

Outline of thesis

The research completed for this thesis was supported by a National Institute for Health Research Doctoral Research Fellowship (DRF-2016-09-086). The scientific abstract of the original Fellowship application is presented in Appendix 3. Funding was awarded on the 11/08/2016. This Fellowship was completed between September 2016 and September 2019.

The findings of the research are presented in 2 parts relating to the two research questions and aims of the study. It principally consists of 4 published and 1 submitted research papers.[2, 28, 33-35]

The final chapter presents a discussion of the findings, considers the strengths and weaknesses of the research and outlines the implications for policy and future research. The thesis content is described in more detail below.

Part 1: An evaluation of the impact of national head injury guidelines in England and Scotland.

Part 1 presents the research conducted which used quasi-experimental methods and complete National Health Service administrative data sets for Scotland and England to address the first research question and aim. This was published in two papers[2, 34] which are reproduced in Chapters 2 and 3. The specific objective of Part 1 was to evaluate the impact of the SIGN and NICE head injury guidelines on hospital admissions head injury and deaths caused by TBI.

When assessing the causal effects of health care interventions, the gold standard method is a randomised control trial.[36] However, the nationwide simultaneous introduction of national head injury guidelines, such as by NICE (England and Wales) and SIGN (Scotland), means this approach is not possible. Interrupted time series analysis is an increasingly popular and recognised quasi-experimental method to assess the effect of health policies introduced at specific time points.[37-39] One significant limitation is possible co-interventions causing some or all of the observed effects. The introduction of the 4-hour ED target at a similar time to the first NICE head injury guidelines is a potential confounder when assessing the impact of the guidelines on hospital admissions. For this reason, the impact of increased CT imaging of minor head injured patients, advocated by both the SIGN and NICE head injury guidelines, on hospital admissions is assessed first using Scottish data (as the SIGN guidelines and 4-hour target were introduced at different time Figure 1.2). The results of this analysis are presented in Chapter 2.

The impact of guideline recommendations for increased imaging and later for management of all patients with severe TBI in specialist neuroscience centres on deaths from TBI was assessed using English data. England, as a larger country, provides a larger sample size and access to individual level data allowed statistical adjustment for changes

in population demographics. The greater number of NICE guidelines iterations also allows the effects of different guideline recommendations to be independently assessed. The results of this analysis are presented in Chapter 3. Chapters 2 and 3 are now summarised in more detail.

Chapter 2: The impact of the SIGN head injury guidelines and NHS 4-hour Emergency Target on hospital admissions for head injury in Scotland: An Interrupted Times Series.

Chapter 2 presents a study assessing the impact of increased CT imaging of head injured patients recommended by successive SIGN head injury guidelines and the 4-hour ED target on hospital admissions.[34] The different time that these intervention were introduced in Scotland provides a unique opportunity to assess their independent effects. Using interrupted time series analysis and aggregated routinely collected NHS data, the impact of these health policies on all admissions for head injury is explored in the period between 1998 and 2016, stratified by guideline recommendation specific age groupings. The study also specifically tests whether an unintended consequence of increased CT imaging of patients with minor head injury is increased hospital admissions for patients with TBI identified radiologically. This is the first study to independently assess the effects of guideline recommended increases in CT imaging and the 4-hour ED target on hospital admissions for head injury using complete national data.

The specific objectives of this study were to:

- Assess the impact of the introduction of the SIGN head injury guidelines and the 4-hour target on the rate of hospital admissions in patients with head injury.
- Explores the extent to which any increase in admissions were due to the identification of more patients with TBI.

Chapter 3: An evaluation of the impact of the NICE head injury guidelines on inpatient mortality from traumatic brain injury: an interrupted time series analysis

Chapter 3 presents research which evaluated the impact of the three iterations of NICE head injury guidelines on inpatient mortality rates from TBI and TBI admission rates in England.[2] The focus of this chapter, unlike the analysis of the Scottish data, is on assessing the impact of the guidelines on outcomes for patients with diagnosed TBI. Trends in TBI deaths and admissions are assessed over the period from 1998 to 2017, using individual patient level NHS administrative data from England to identify individual cases of TBI. Interrupted time series analysis with adjustment using individual level data for changes in population characteristics over time was used to assess for effects associated with guideline implementation. As individual level data was not available for Scotland, such analysis was only possible in the English data set. The effect of the first guideline on inpatient TBI mortality rates is compared with a later guideline. The first NICE guideline primarily recommended increased CT imaging, whilst the later guideline also recommended the management of patients with severe TBI in specialist centres. Analysis is stratified into three age categories based on age group specific guideline recommendations. This is the first time that the effect of national head injury guidelines' on TBI mortality has been evaluated using complete national data and interrupted time series analysis.

The specific objective of this study was to:

- Evaluate the impact of the NICE head injury guidelines on deaths and hospital admissions caused by traumatic brain injury

Part 2: Developing a predictive model for deterioration in alert TBI patients with injuries identified by CT imaging

Part 2 of this thesis describes the research conducted to derive a prognostic model to try and predict risk of deterioration in initial GCS13-15 patients with TBI identified by CT imaging. Part 2 includes 3 chapters: a published systematic review of risk factors for

deterioration in mTBI patients with injuries identified by CT,[28] a published study protocol for developing a prognostic model in a retrospective cohort of this population of TBI patients[33] and the results of the prognostic modelling study (under review).

Chapter 4: The risk of deterioration in GCS13-15 patients with traumatic brain injury identified by CT imaging . A systematic review and meta-analysis.

This chapter presents a systematic review and meta-analysis which summarises and synthesises existing literature that assesses the risk that mTBI patients with injuries identified by CT imaging have of clinically important deterioration and identifies risk factors for deterioration. The review protocol and reporting followed international standards for systematic reviews.[40] Estimates of rates of deterioration were pooled across studies for: any form of clinical deterioration, neurosurgical intervention and death, in this mTBI population. Meta-regression was used to explore between-study variation in outcome estimates using study population characteristics to identify risk factors for deterioration. In addition, where multiple studies presented individual risk factor effect estimates for deterioration, they were pooled. Factors identified as potentially affecting deterioration in this review were used as candidate variables on which to collect data in the prognostic retrospective cohort study.

The specific objectives of this review were to:

- Estimate the overall risk of adverse outcomes in patients who are initially GCS13-15 in the ED when traumatic brain injury is identified by CT imaging.
- Assess which prognostic factors affect the risk of deterioration and other clinically important outcomes in this population.

Chapter 5: A protocol for the development of a prediction model in Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge?

Chapter 5 presents a published protocol for a retrospective cohort study based on case review that was conducted to develop a prognostic model for predicting risk of deterioration in GCS13-15 patients with TBI identified on CT imaging. The study was designed in adherence to international standards for prognostic research.[41] Data collection was completed at the two English Major Trauma centres described in the protocol and a third major trauma centre added later during data collection to help achieve the required sample size and increase generalisability.

The protocol presents an *a priori* justification for: the retrospective study design, methods for handling missing data, sample size, statistical methods for model development and internal validation techniques. This includes outlining the use of logistic regression to model a composite outcome of deterioration as binary dependent variable and stepwise backward elimination to select a parsimonious final multivariable model.

Chapter 6: Development of a clinical decision rule for the early safe discharge of patients with mild traumatic brain injury and findings on CT brain scan: a retrospective cohort study.

Chapter 6 presents the results of the study including: the derived models predicting different outcomes of deterioration, measures of optimism adjusted model performance and results of implementing a decision rule for discharge of patients from the ED derived from the prognostic model. In addition, for the first time in the UK, the performance of the BIG criteria (used in the USA to select patients for discharge from the ED) is assessed in the study cohort.

The specific aims of prognostic modelling study were to:

- Estimate the prevalence of clinically important deterioration in GCS13–15 patients with traumatic CT abnormalities.
- Develop prediction models for patient deterioration that could be used to help hospital admission and specialist referral decision-making.

- Compare the performance of the derived prediction model with the BIG criteria.

Chapter 7: Discussion

Chapter 7 presents the overall findings of the research conducted and discusses how these findings relate to each other and existing research. This is a synthesis of the individual components of this thesis where areas highlighted in the discussion in each chapter are drawn together to present and assess the totality of the research. The strengths and weakness of the completed research are evaluated and suggestions for how the research could be improved are made. The implications of the thesis for future research, clinical practice and health policy are then discussed.

Part 1: An evaluation of the impact of national head injury guidelines in England and Scotland.

Introduction:

A series of national (SIGN and NICE) head injury guidelines were introduced in Scotland and England from 2000 with aim of simultaneously improving outcomes for patients with TBI and reducing inpatient hospital admission for patients presenting to the ED with head trauma. National evaluation of the impact of these guidelines using NHS administrative datasets and the quasi experimental method of interrupted time series has not been previously undertaken. The limited available previous evidence indicates that increased management of TBI patients with severe injuries recommended by the second NICE guideline may have reduced TBI deaths.[23] There is also some evidence that an unintended consequence of increased CT imaging (recommended by all head injury guidelines) may be an increase in hospital admissions due to increased radiological diagnosis of TBI.[18]

This part of the thesis presents two chapters consisting of word versions of published papers that evaluate the impact of national head injury guidelines on hospital admissions for head trauma and deaths from TBI.[2, 34] Together these chapters address the first research question and aim of this thesis. The impact of national head injury guidelines on hospital admissions is assessed in Scotland, as in England the 4-hour ED target was introduced at the same time point as the first NICE head injury guideline, whilst in Scotland equivalent SIGN head injury guidelines were introduced at a different time. This allows the independent effects of these policies to be evaluated on admissions for a population of all head injury patients which increased diagnostic precision through increased CT imaging was intended to reduce admissions of.

The analysis of the English data is primarily intended to assess whether the introduction of the NICE guidelines was associated with a reduction in TBI mortality and affected TBI admissions. The individual level data available for England meant that deaths attributable

to TBI could be accurately identified and adjustment for demographic factors could also be completed. The results of this evaluation of the impact of Scottish SIGN guidelines is presented in Chapter 2 and the results of the evaluation of the impact of NICE guidelines in England in Chapter 3.

Method and data sets:

Interrupted time series analysis is used in the research presented in chapters 2 and 3 to evaluate the impact of the NICE and SIGN head injury guidelines. This is a recognised quasi-experimental approach to investigate the causal effects of health policies introduced at specific time points on outcomes collected at regular time intervals.[37] The exact statistical methods and outcomes assessed are presented in the methods sections of Chapters 2 and 3. Appendix 4 presents a full summary of data acquisition, governance and handling.

The data used for evaluating the impact of the SIGN Head Injury guidelines on hospital admissions in Scotland was provided by Information Service Division (ISD) Scotland on 15/12/2016. The data provided were aggregated monthly totals of admissions with ICD10 coding related to head injury along with aggregated numbers of associated deaths and neurosurgical procedures. Small numbers were suppressed by ISD Scotland in accordance with NHS guidelines. The aggregated nature of these data meant they were completely non-identifiable and therefore not did require a specific data sharing agreement to access or specific information governance procedures for storage.

Individual patient level Office of National Statistics (ONS) linked Hospital Episode Statistics for all hospitals in England was used for the analysis of trends in England. This data set was anonymised but as it contained individual patient level data access required a specific data sharing agreement and storage in a way that complied with an NHS information governance Tool Kit. The joint nature of Hull York Medical School meant that the NIHR Doctoral Research Fellowship funding was administered by the University of Hull but the NHS Information Governance Tool Kit was available at the University of York. Therefore, a data sharing agreement was required between these two Universities. Access for the data

extract used in this part of the project was fist applied for in October 2016 and it was provided in April 2018. These data are currently being stored (in compliance with an NHS digital data sharing agreement which expires in April 2020) in an isolated secure server at Health Sciences at the University of York and will be destroyed in compliance with NHS digital guidelines at the end of this agreement.

Chapter 2: The impact of the SIGN head injury guidelines and NHS 4-hour Emergency Target on hospital admissions for head injury in Scotland: An Interrupted Times Series.

Chapter Introduction

This chapter presents the text of a paper published in the BMJ Open in December 2018.[34] The text is identical to that published except for refence, table and figure numbers. Supplementary Material are presented in the thesis appendices and references to these materials have been changed in accordance with this.

Abstract

Objectives:

Head injury is a common reason for Emergency Department (ED) attendance. Around 1% of patients have life-threatening injuries, whilst 80% of patients are discharged. National guidelines (SIGN) were introduced in Scotland with the aim of achieving early identification of those with acute intracranial lesions yet safely reducing hospital admissions.

This study aims to assess the impact of these guidelines and any effect the national 4-hour ED performance targets had on hospital admissions for head injury.

Setting:

All Scottish hospitals between April 1998 and March 2016.

Participants:

Patients admitted to hospital for head injury or traumatic brain injury (TBI) diagnosed by CT imaging identified using administrative Scottish Information Services Division data. There are 275 hospitals in Scotland. In 2015/2016 there were 571, 221 emergency hospital admissions in Scotland.

Interventions:

The SIGN head injury guidelines introduced in 2000 and 2009. The 4-hour ED target introduced in 2004.

Outcomes:

The monthly rate of hospital admissions for head injury and traumatic brain injury.
Study Design:

An interrupted time series analysis.

Results:

The 1st guideline was associated with a reduction in monthly admissions of 0.14 (95% CI:0.09 to 4.83) per 100, 000 population. The 4-hour target was associated with a monthly increase in admissions of 0.13 (95% CI:0.06 to 0.20) per 100, 000 population. The 2nd guideline reduced monthly admissions by 0.09 (95% CI:-0.13 to -0.05) per 100, 000 population. These effects varied between age groups.

The guidelines were associated with increased admissions for patients with injuries identified by CT imaging- Guideline 1: 0.06 (95% CI: 0.004 to 0.12); Guideline 2: 0.05 (95% CI: 0.04 to 0.06) per 100 000 population.

Conclusion:

Increased CT imaging of head injured patients recommended by SIGN guidelines reduced hospital admissions. The 4-hour ED target and the increased identification of TBI by CT imaging acted to undermine this effect.

Strengths and limitations of this study:

This is the first study to assess the impact of the SIGN head injury guidelines and 4-hour Emergency Department target on hospital admissions for head injury.
We used the robust method of interrupted time series analysis and found the SIGN guidelines acted to reduce hospital admissions, but the 4-hour target increased hospital admissions.

Due to the aggregated nature of the available data we were unable to perform some age group specific and injury sub-group sensitivity analysis.

Authors' contributions

I conceived the idea for this study with help from my supervisors Trevor Sheldon, Fiona Lecky and Victoria Allgar and this formed part of my NIHR Doctoral Research Fellowship application . I completed all the analysis with help from Elaenor Morris, a Medical Student who completed a summer research project with me. My supervisors Trevor Sheldon and Victoria Allgar provided specialist advice regarding interrupted time series analysis. My supervisor, Fiona Lecky provided specialist advice regarding the clinical context and interpretation of the results. All authors read and approved the final manuscript.

Background:

There are 1.4 million annual attendances to Emergency Departments (ED) in England and Wales following a head injury (blunt trauma to the head).[1] In Scotland an estimated 6.6% of ED attendances are for head injury.[11] Approximately 95% of patients present with an initial Glasgow Coma Scale (GCS) of 13-15, indicating normal or minimally impaired conscious level and are defined as having a minor head injury.[1, 6]

Around 1% of minor head injured patients have life-threatening traumatic brain injuries (TBI) (injury to the brain/ functional impairment due to external force) but this may not be initially clinically apparent.[1] Early identification of severe TBI can facilitate life-saving neurosurgery.[4] The clinical challenge is to differentiate patients with life-threatening TBI who present with a high conscious level from patients who can be discharged safely. This can be achieved through observation for deterioration or cranial CT imaging.[17] The health services challenge is finding a way of differentiating these groups in a way that minimises unnecessary imaging or inpatient hospital admissions of patients without clinically important TBI. Research has focused on developing clinical decision rules that, using clinical assessment, select patients at risk of life-threatening TBI for CT imaging and allow the discharge of low-risk patients. The most validated, in adults, is the Canadian CT Head Rule (CCHR) and this forms the basis of the Scottish Intercollegiate Guidelines Network (SIGN) and English National Institute for Health and Care Excellence (NICE) head injury guidelines.[1, 9, 11] The 2nd SIGN guideline contains specific paediatric indications for CT imaging influenced by the CHALICE rule, which was derived in a population of head injured children.[2]

Two iterations of the SIGN guidelines have been introduced (Fig. 2.1).[10, 11] The first recommended increased CT imaging of head injured patients but still featured a role for skull x-rays and admission for observation.[10] The 2nd SIGN guideline extended CT imaging further.[11] A study assessing trends in hospital admissions for TBI in Scotland between 1998 and 2009 found changes in rates of admissions at specific time points after 2000, but the analysis was data driven and does not explicitly assess the impact of the SIGN guidelines.[42] Implementation studies of NICE head injury guidelines in England suggested

that the cost of increased CT imaging (£100 per scan) would be offset by a reduction in inpatient hospital admissions (£847 per admission) as patients admitted for observation would be dicharged from the ED following normal CT imaging, preventing many admissions.[15, 16, 43]

However, a study using English Hospital Episodes Statistics (HES) found head injury inpatient admissions increased following the introduction of the NICE guidelines, possibly due to the near simultaneous introduction of the 4-hour ED target. Appendix 1 presents the details of the 4-target and in 2002 around 23% of all patients in the UK remained in the ED for longer than 4-hours.[19] The target could act to incentivise inpatient admissions for patients at medium risk for TBI, who require imaging within 8 hours, to avoid breaches. Previously they would have been imaged in the ED and the majority discharged. A further cause of increased admissions could be the detection of brain injuries previously not identified, some without clinically significant sequelae, due to increased imaging.[18] In Scotland the 4-hour target was not introduced at the same time as the SIGN guidelines. This provides a unique opportunity to assess the independent effects of these policy interventions.

Aims:

This study aims to assess the impact of the introduction of the SIGN head injury guidelines and the 4-hour target on the rate of hospital admissions in patients with head injury and explores the extent to which any increase in admissions were due to the identification of more TBI.

Methods:

Study Design:

Interrupted time series analysis is an established and robust method for the evaluation of health policies implemented at discrete time points.[38, 39]

Dataset:

The Scottish Information Services Division (ISD) contains a repository of information routinely collected at discharge from hospital for all non-obstetric and non-psychiatric inpatient hospital admissions in Scotland (including most short stay admissions to Clinical Decision Units) . Since 1996 reason for admission has been categorised using ICD10 diagnostic coding and since 1989 interventions have been coded using the OPSC4 classification.[44-46] This repository was used, for the period 1998-2016, to generate monthly numbers of: patients admitted with ICD10 coding for head injury, patients admitted with ICD coding indicating TBI identified by CT imaging, neurosurgical interventions and deaths within 30 days of admission for patients with CT evidence of TBI. Diagnostic codes were counted if they were either primary or secondary diagnoses.

The data extract used for analysis is available from ISD Scotland for a commercial fee. The data set was fully anonymised and aggregated with small numbers suppressed.

We selected an ICD10 code subset definition of head injury that includes all possible definitions of TBI and head injury (Table 2.1). The ICD10 codes used are consistent with those selected to explore the NICE guideline's effect on hospital admissions for head injury, with the addition of codes for crush injuries.[18] We selected an ICD10 code subset to define TBI that corresponds to injuries identified by CT imaging including codes for traumatic intra-cranial haemorrhages and skull fractures, but excluded codes for concussion and other clinical diagnoses (Table 2.1).

Outcomes:

Admissions for head injury:

The monthly number of patients admitted to hospital with one or more ICD10 code indicating head injury between April 1998 and March 2016 was generated by the ISD. As the SIGN guidelines have specific recommendations regarding paediatric patients and

patients 65 and over, admissions were stratified into: 0-15, 16-64 and ≥65 age groupings. Yearly and monthly number of admissions were converted into a rate per 100, 000 population using Nomis Office of National Statistics (ONS) mid-year population estimates for Scotland for each age grouping (Appendix 5).

Admissions for Traumatic Brain Injury:

The ISD generated the monthly number of patients admitted to hospital with at least one ICD10 code sub-classification indicting an admission for TBI. Monthly and yearly rates per 100, 000 population of admissions for TBI were calculated using Nomis ONS mid-year Scottish population estimates.

The ISD also provided the monthly number of patients admitted with an ICD10 code indicating TBI that had one or more OPSC4 neurosurgical codes (Table 2.2). A monthly proportion of admissions for TBI that resulted in neurosurgery was estimated. The small number of monthly TBI admissions prevented release of data stratified by age group.

Table 2.1: Annual trends admissions for head injury and TBI

Year	Annual rates head injury admissions per 100, 000 population each age group.*				Annual rates TBI admissions per 100, 000 population all age.** (Percentage annual rate all head injury admissions)
	All ages	0-15	16-64	65+	
1999	484	558	453	536	77 (15.9%)
2000	476	519	449	556	70 (14.7%)
2001	493	561	457	578	72 (14.6%)
2002	489	556	447	598	71 (14.5%)
2003	451	521	404	581	76 (16.9%)
2004	435	495	381	589	82 (18.9%)
2005	417	497	350	591	78 (18.7%)
2006	427	477	369	585	79 (18.5%)
2007	442	441	393	653	79 (17.9%)
2008	435	400	386	670	76 (17.4%)
2009	440	406	377	709	79 (18%)
2010	400	361	337	709	80 (20%)
2011	421	369	352	741	91 (21.6%)
2012	411	339	321	817	89 (21.7%)
2013	396	307	293	845	97 (24.5%)
2014	385	319	268	848	102 (26.5%)
2015	373	316	251	867	123 (33%)

*ICD10 codes for head injury: S00-S09, T04.0 and T06.0

** ICD10 codes for TBI: S02.0, S02.1, S02.7, S02.8, S02.9, S06.1, S06.3, S06.4, S06.5, S06.6, S06.7, S06.8, S06.9, T04.0 and T06.0

Table 2.2: Impact of the SIGN guidelines on number of admissions and deaths from Traumatic Brain Injury per 100, 000 Scottish population

Outcome	Winter Effect	Initial Trend	1st SIGN Guideline	4-hour Target Introduced	2nd SIGN Guideline	Durbin-Watson Statistic
Admissions for TBI/100 000		-0.04 (95% CI: -0.09 to 0.004) P=0.07	**Change level:** 0.26 (95% CI:- 0.74 to 1.26) P=0.61	**Change level:** 0.16 (95% CI: -0.67 to 0.99) P=0.71	**Change level:** -0.39 (95% CI: -1.09 to 0.30) P=0.27	Untransformed 1.46 Prais-Winsten 2.02
			Change trend: 0.06 (95% CI: 0.004 to 0.12) P=0.04	**Change trend:** -0.02 (95% CI: -0.05 to 0.01) P=0.24	**Change trend:** 0.05 (95% CI: 0.03 to 0.07) P<0.01	
Percentage TBI admissions neurosurgical+		0.05 (95% CI: -0.01 to 0.11) P=0.10	**Change level:** -0.64 (95% CI: -1.83 to 0.56) P=0.29		**Change level:** 0.47 (95% CI:-0.17 to 1.12) P=0.15	Untransformed 1.81
			Change trend: -0.06 (95% CI: -0.12 to 0.001) P=0.047		**Change trend:** -0.01 (95% CI:-0.03 to -0.003) P=0.01	
Deaths/100 000	0.03 (95% CI: 0.001 to 0.07) P=0.04	-0.001 (95% CI:-0.004 to 0.002) P=0.57	**Change level:** -0.02 (95% CI:- 0.09 to 0.06) P=0.62		**Change level:** -0.01 (95% CI:-0.06 to 0.05) P=0.85	Untransformed 2.3
			Change trend: 0.001 (95% CI:-0.002 to 0.005) P=0.44		**Change trend:** 0.0004 (95% CI: -0.001 to 0.001) P=0.46	
Percentage TBI admissions death	0.88 (95% CI: 0.36 to 1.41) P<0.01	0.03 (95% CI: -0.03 to 0.10) P=0.35	**Change level:** -0.79 (95% CI: -2.12 to 0.54) P=0.24		**Change level:** 0.52 (95% CI: -0.32 to 1.35) P=0.22	Untransformed 2.08
			Change trend: -0.03 (95% CI: -0.10 to 0.03) P=0.33		**Change trend:** -0.03 (95% CI: -0.04 to -0.01) P<0.01	

+ Neurosurgical procedure defined as 1 or more OPSC4 codes: A05.2, A05.3, A05.4, A05.8, A05.9, A40.1, A40.8, A40.9, A41.1, A41.8, A41.9, V03.1, V03.2, V03.4, V03.6, V03.7, V03.8, V03.9, V05.3 and V05.4

Deaths related to Traumatic Brain Injury:

The ISD provided the monthly number of patients who died within 30 days of admission with at least one ICD10 code for TBI. This was converted into a rate using Nomis ONS mid-year Scottish population estimates. The monthly proportion of patients admitted with TBI who died within 30 days of admission was estimated using the total number of monthly admissions for ICD10 codes that corresponded to TBI.

Statistical analysis:

A monthly time series of the rate of inpatient hospital admissions for head injury ICD codes was plotted from April 1998 to March 2016. An interrupted times series analysis was completed assessing the impact of SIGN head injury guidelines and the 4-hour ED target using the ITSA package in STATA 14.[47 48] The model included 3 intervention time points: the introduction of the 1st SIGN guideline in August 2000, the introduction of the 4-hour target in 2004 and the introduction of the 2nd SIGN guideline in May 2009. Analysis was stratified into 3 age groups: 0-15, 16-64 and ≥65s. A segmented regression model predicting the rate of hospital admissions per 100, 000 population in each age grouping per month was estimated.[38]

Autocorrelation of the residuals was assessed using the Durbin-Watson and Rho statistic.[38, 49] Where there was sufficient deviation from a Durbin Watson statistic of 2 and the Rho statistic was not statistically significant, the Prais-Winsten transformation was used to adjust for auto-correlation.[38] Seasonality was assessed by introducing a dummy variable to the model in which winter months (December, January and February) were coded 1 and was included in the model when a statistically significant predictor.

The interrupted time series analysis was repeated to assess: the impact of the SIGN guidelines and 4-hour target on the rate of hospital admissions for patients with an ICD10 code indicating TBI, the impact of SIGN guidelines on the proportion of inpatient admissions for TBI that resulted in neurosurgery or death and the death rate within 30 days of admission for TBI. It was thought a priori that the 4-hour target would not

plausibly have affected neurosurgery or deaths. This was confirmed through visual inspection and was excluded from analysis of these outcomes.

Estimates of the impact of the policy interventions on inpatient admissions were made by using the pre-intervention model to estimate hypothetical monthly rates of admissions if no intervention had occurred. These were subtracted from the monthly admission rates estimated by the post-intervention model.[39] To explore any effect of a policy implementation lag a sensitivity analysis was performed for all the models in which the 12 months immediately following the introduction of a policy change, were excluded from analysis.[38]

Patient and Public Involvement

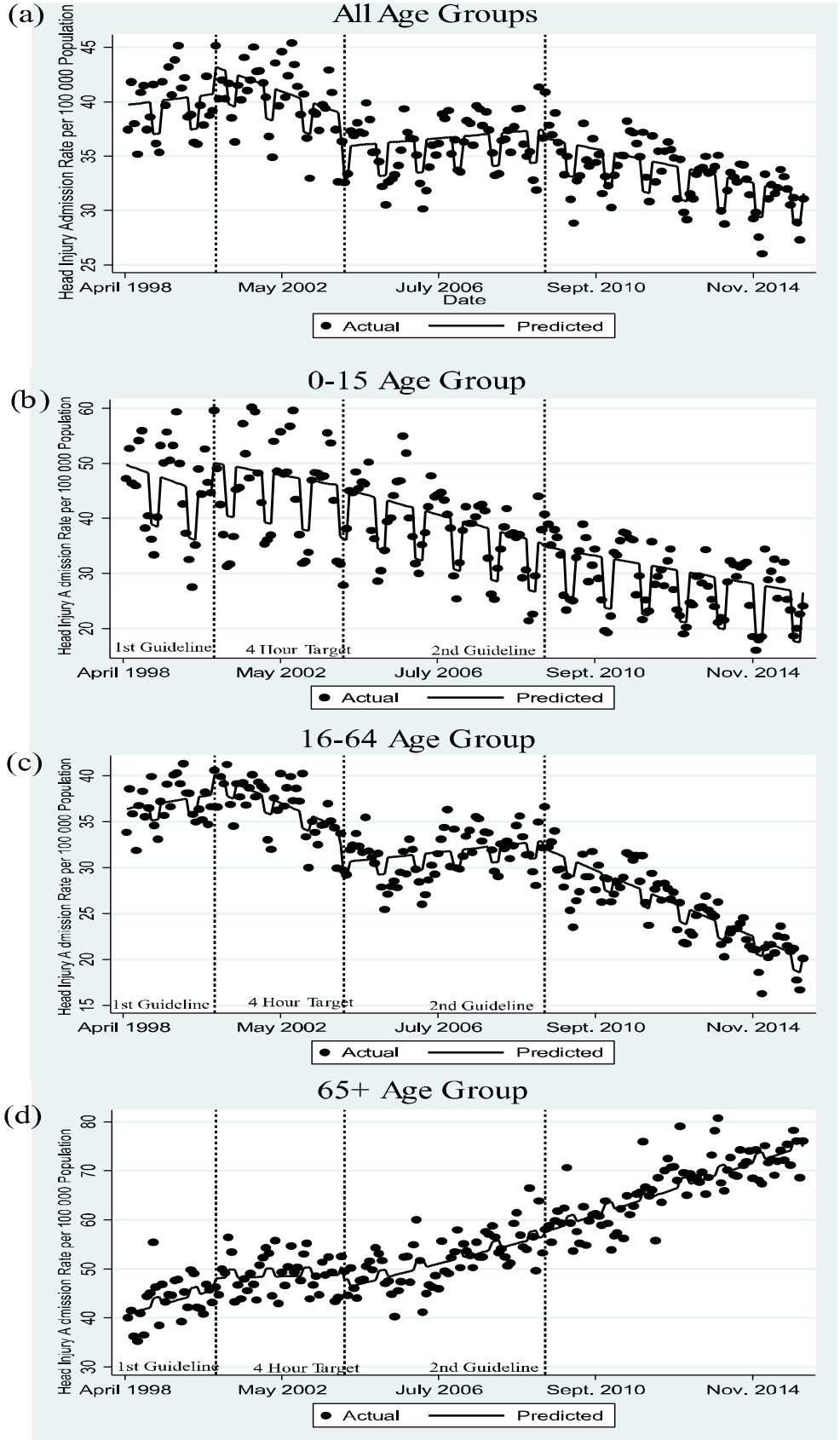
The Hull and East Yorkshire NHS Trust Trans-Humber Consumer Research Panel and Hull branch of the Headway charity were consulted in the initial stages of developing the research questions addressed in this study. These patient groups highlighted that although national head injury guidelines seemed evidence based, there appeared to be little evidence to show they had achieved their aims.

Results:

Head injury inpatient hospital admissions:

Table 2.1 show yearly rates of inpatient hospital admissions. Fig. 2.1 and Table 2.3 present the results of the interrupted time series assessing the impact of the SIGN guidelines and 4-hour ED target on monthly head injury admissions. Admission rates and estimates of effect are reported per 100, 000 population in each age grouping. The SIGN guidelines and 4-hour target were associated with a significant change in the total level and trend of the rate admissions for head injury (Fig 2.1a). The effect varied between age group.

Figure 2.1: The Impact of the 4-hour target and SIGN guidelines on head injury admissions



0-15 Age Group:

Monthly inpatient admissions fell from 47.18 to 24.02 per 100, 000 per month over the time period (Fig. 2.1b). Neither SIGN guideline nor the introduction of the 4-hour target significantly affected the underlying reducing trend in hospital admissions but the first guideline was associated with a borderline statistically significant increase in level (6.06; 95% CI: -0.49 to 12.62) (Table 2.3). Admissions were less likely to occur in winter months (-9.19; 95% CI: -10.81 to -7.57) (Table 2.3).

16-64 Age Group:

Inpatient admissions fell from 36.39 to 20.20 per 100, 000 per month from April 1998 to March 2016 (Fig 2.1c). Before the 1st SIGN guideline hospital admissions were increasing monthly (0.04; 95% CI: -0.08 to 0.15) (Table 2.3 and Fig. 2.1c). The 1st guideline was associated with a declining monthly trend in admissions (-0.20; 95% CI:-0.35 to -0.05). The 4-hour target was associated with an initial fall in the number of inpatient admissions (-3.54; 95% CI: -5.76 to -1.33) but subsequent trend of increasing monthly admissions (0.18; 95% CI: 0.10 to 0.27). The 2nd guideline was associated with a return to a declining trend in admissions (-0.18; 95% CI:-0.23 to -0.13). Inpatient admissions were reduced in winter months (-1.74; 95% CI:-2.48 to -1.01).

The trend following the introduction of the 1st SIGN guideline hypothetically continued in the period after the introduction of the 4-hour target is shown in Appendix 6. By subtracting this from the model that incorporated the introduction of the 4-hour target and the 2nd SIGN guideline we estimate that from January 2004 to March 2016 the introduction of the 4-hour target was associated with an additional 745 hospital admissions per 100 000 population aged 16-64.

≥65 Age Group:

Monthly admissions increased from 40.00 to 76.09 over the time period (Fig. 2.1d). The only statistically significant change in the underlying trend was at the introduction of the 4-hour target which was associated with an acceleration in the increase in hospital admissions (0.15; 95% CI: 0.01 to 0.28) (Table 2.3 and Fig. 2.1d). Winter months were associated with increased hospital admissions (1.67; 95% CI: 0.32 to 3.02).

Sensitivity Analysis for 12-month implementation lag:

The introduction of an intervention lag in the model (Appendix 7) did not materially affect estimates of effect associated with interventions.

Inpatient hospital admissions for Traumatic Brain Injury on CT scan:

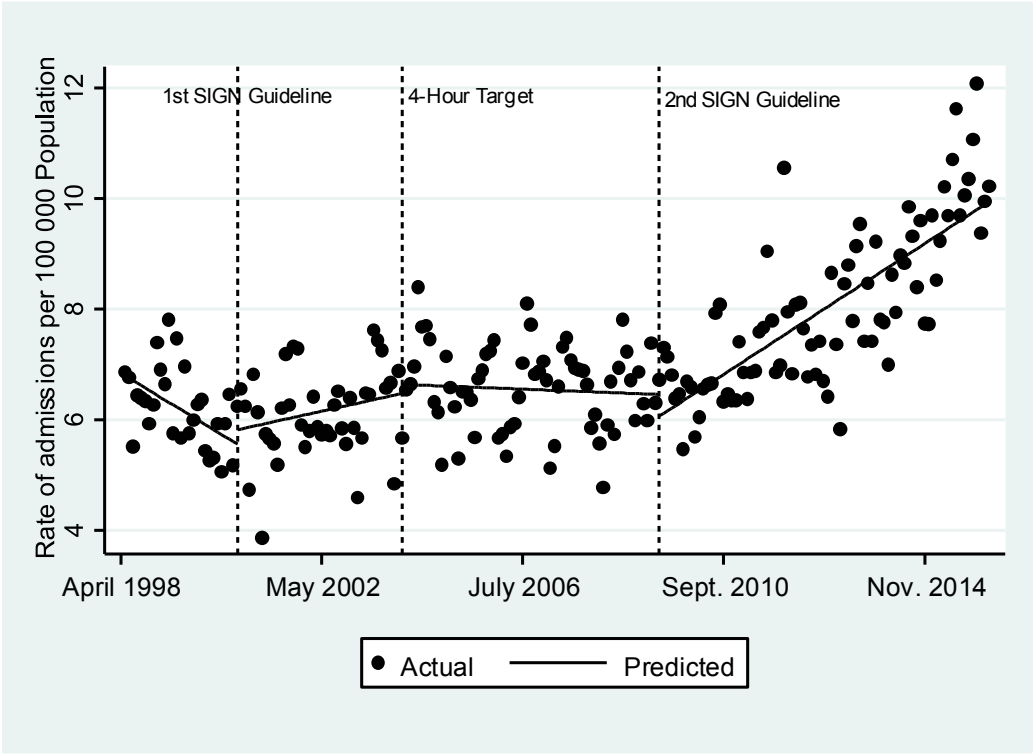
Admission per 100, 000 per month increased from 6.85 to 10.21 over the time period (Fig. 2.2). Before the 1st SIGN guideline hospital admissions were decreasing (-0.04; 95% CI:-0.09 to 0.004) (Table 2.2 and Fig. 2.2). The introduction of the 1st guideline was associated with a trend of increasing admissions (0.06; 95% CI: 0.004 to 0.12). The 4-hour target was not associated with a significant change in level or trend. The introduction of the 2nd SIGN guideline was associated with an acceleration in the increase in admissions (0.05; 95% CI: 0.04 to 0.06).

Comparing admissions for TBI that would have occurred if the 2nd SIGN guideline had not been introduced with the empirically derived model indicates that from May 2009 to March 2016 the introduction of the 2nd SIGN guideline was associated with an additional 138 hospital admissions per 100, 000 population (Appendix 8).

Table 2.3: Impact of the SIGN guidelines and introduction of 4-Hour ED Target on number of Head Injury Admissions per 100, 000 Scottish population by age group

Age Band	Winter Effect	Initial Trend	1st SIGN Guideline	4-hour Target Introduced	2nd SIGN Guideline	Durbin-Watson Statistic
All ages	-3.00 (95% CI:-3.78 to -2.30) P<0.01	0.04 (95% CI: -0.08 to 0.15) P=0.53	**Change level:** 2.45 (95% CI:0.09 to 4.83) P=0.04	**Change level:** -2.89 (95% CI:-4.84 to -0.95) P<0.01	**Change level:** -0.84 (95% CI:-2.50 to 0.78) P=0.31	Untransformed 1.68 Prais-Winsten 2.02
			Change trend: -0.14 (95% CI: -0.27 to -0.01) P=0.03	**Change trend:** 0.13 (95% CI: 0.06 to 0.20) P<0.01	**Change trend:** -0.09 (95% CI:-0.13 to -0.05) P<0.01	
0-15	-9.19 (95% CI: -10.81 to -7.57) P<0.01	-0.21 (95% CI: -0.53 to 0.12) P=0.22	**Change level:** 6.06 (95% CI:-0.49 to 12.62) P=0.07	**Change level:** -0.41 (95% CI: -5.98 to 5.17) P=0.89	**Change level:** -0.54 (95% CI:-5.31 to 4.22) P=0.82	Untransformed 1.34 Prais-Winsten 1.87
			Change trend: -0.10 (95% CI:-0.29 to 0.49) P=0.61	**Change trend:** -0.05 (95% CI: -0.27 to 0.16) P=0.63	**Change trend:** 0.06 (95% CI:-0.07 to 0.18) P=0.37	
16-64	-1.75 (95% CI:-2.48 to -1.01) P<0.01	0.06 (95% CI: -0.07 to 0.19) P=0.39	**Change level:** 2.12 (95% CI:-0.54 to 4.79) P=0.12	**Change level:** -3.54 (95% CI:-5.76 to -1.33) P<0.01	**Change level:** -0.87 (95% CI: -2.74 to 0.99)P=0.36	Untransformed 1.45 Prais-Winsten 2.10
			Change trend: -0.20 (95% CI: -0.35 to -0.05) P<0.01	**Change trend:** 0.18 (95% CI: -0.10 to 0.27) P<0.01	**Change trend:** -0.18 (95% CI:-0.23 to -0.13)P<0.01	
65+	1.67 (95% CI: 0.32 to 3.02) P=0.02	0.17(95% CI: -0.04 to 0.39) P=0.11	**Change level:** 2.28 (95% CI: -2.13 to 6.86) P= 0.30	**Change level:** -2.70 (95% CI: -6.39 to 0.99) P=0.15	**Change level:** 0.85 (95% CI:-2.22 to 3.93)P=0.59	Untransformed 1.70 Prais-Winsten 2.00
			Change trend: -0.16 (95% CI: -0.40 to 0.09) P=0.21	**Change trend** 0.15 (95% CI: 0.01 to 0.28) P=0.03	**Change trend:** 0.05 (95% CI: -0.03 to 0.12) P=0.23	

Figure 2.2: The impact of the SIGN guidelines and 4-Hour Target on admissions for Traumatic Brain Injury



Both SIGN guidelines were associated with a reduction in trend in the percentage of TBI admissions resulting in neurosurgery: 1st guideline (-0.06; 95% CI: -0.12 to 0.001) and 2nd guideline (-0.01; 95% CI: -0.03 to -0.003) (Table 2.2 and Appendix 9). A 12-month implementation lag did not materially affect the estimates (Appendix 10).

Deaths following admission for TBI:

Neither guideline was associated with a change in level or trend in monthly death rate within 30 days of admission with an ICD 10 code indicating TBI (Table 2.2 and Appendix 11). The introduction of the 2nd SIGN guideline was associated with a significant reduction in the underlying trend in the monthly percentage of inpatient admissions for TBI that resulted in death within 30 days (-0.03; 95% CI: -0.04 to -0.01) (Table 2.2 and Appendix 12).

Introduction of a 12-month implementation lag into the models did not materially change the estimates (Appendix 13).

Discussion:

Summary:

To our knowledge, this is the first study to evaluate the impact of the SIGN guidelines and the 4-hour ED target on head injury hospital admissions. We found evidence that the SIGN guidelines reduced inpatient admissions, the effect varying by age group. In the 16-64 age group both guidelines were associated with a reduction in hospital admissions (Fig. 2.1c and Table 2.3). This may be due to increased CT imaging in the ED identifying more patients without TBI safe for discharge. In the paediatric population there was an underlying trend of reducing hospital admissions that the guidelines did not appear to affect. In the ≥65 age group neither SIGN guideline iteration acted to offset the secular trend of increasing hospital admissions. Inpatient admissions increased in winter months in the ≥65 age group but were reduced in other age groups. Falls from standing are known to be the most common cause of brain injuries in those ≥65, whilst assault and

road traffic accidents are more common causes of injuries in younger patients.[8] Weather conditions during winter may increase the likelihood of falls from standing whilst reducing the prevalence of assault or road traffic accidents.[50]

The introduction of both SIGN guideline iterations were associated with an increased in hospital admissions for patients with TBI and a reduction in the proportion of inpatient admissions that resulted in neurosurgery or death (Table 2.2). The guidelines may have acted, as previously hypothesised, to increase CT diagnosis and admissions of patients with brain injuries of lower severity who do not require intervention.[18] The 4-hour target was associated with an increase in hospital admissions for adults (Fig. 2.1c, 2.1d and Table 2.3). This effect was reversed by the 2nd SIGN guideline in the 16-64 but not the ≥65 age group.

The 4-hour target's effect on adult head injury hospital admissions appears related to the time from admission which CT imaging is recommended . The 1st guideline contained no recommendation for when CT imaging should occur. The introduction of the 4- hour ED target increased head injury hospital admissions in both the 16-64 and ≥65 age groupings, presumably as patients were admitted to await imaging to comply with the target. The 2nd SIGN guideline increased the indications for immediate CT imaging in the 16-64 age group and was associated with a downward trend in admissions. A reduction in hospital admissions was not observed in the ≥65 age group following the 2nd SIGN guideline. The 2nd SIGN guideline includes a series of specific additional indications for imaging in the ≥65 age group that are recommended to occur within 8 hours of ED attendance. As 8 hours is longer than the 4-hour target patients with these indications for CT imaging would be admitted to hospital. This may account for why the 2nd SIGN guideline was not associated with reduced hospital admissions for those ≥65.

Strengths:

We have used a time series of 216 data points and followed established techniques to control for seasonal factors and auto-correlation.[38] We have adjusted for population

factors using mid-year population estimates that incorporate the changing demography of Scotland's population. The models constructed were robust to sensitivity analysis for time lags.

There is controversy regarding which ICD10 codes correspond to clinical definitions of head injury and TBI with inconsistent sets of ICD10 codes used to encompass both.[51] We selected subsets of codes for head injury that are likely to be sensitive to changes in admission practice related to increased diagnostic precision of TBI from increased CT imaging and inpatient admissions of patients awaiting an exclusion of TBI due to the 4-hour target. Our ICD10 code selection for TBI was intended to encompass radiologically detected injuries as this outcome would be sensitive to increased diagnoses of TBI by CT imaging.

Weaknesses:

Ideally the effects of guideline implementation and policy interventions would be assessed using randomised control trials. However, interrupted time series analysis (a rigorous quasi-experimental study design) is becoming increasingly popular particularly for the evaluation of health care practice, programmes and policy because it allows causal inferences when interventions are introduced at specific time points. Discontinuities in outcomes, observed at or shortly after the time of intervention, constitute persuasive evidence of an effect with high internal and external validity.[37-39, 52] The method has limitations notably the potential for observed discontinuities to result from co-interventions instead of the health policies under investigation. We cannot find other policies or sudden changes to the population of Scotland that could account for the observed changes in admissions for head injury in Scotland at the time of the either the introduction of the SIGN guidelines or the 4-hour ED target.

This study used routinely collected Scottish Information Services Division (ISD) data, and administrative data should be approached with some caution.[53] There may be inaccuracies in diagnostic codes due to coding errors. However, there were no changes to

the cohort of admitted patients that data was collected on during the study period and ISD data has been found to be both sufficiently reliably and comprehensively collected to support its use in research.[54, 55] Furthermore, random poor coding, without changes in coding practice, are unlikely to result in sharp discontinuities at the specific time points of the policies considered here. ICD coding changed in 1996, so we only used ISD data from 1998 to give time for adjustment. This limited the number of data points before the 1st SIGN guideline, so we may have lacked the power to detect some changes associated with the 1st guideline as statistically significant (Table 2.3 and Fig. 2.1).

We could not stratify all the analysis by age group as the small number of some outcomes prevented release of aggregated data. A sensitivity analysis using ICD10 injury subtypes was also not possible due to the aggregated nature of the available data. A more sensitive outcome measure for changes in admission practice due to either the SIGN guidelines or 4-hour target may be the proportion of attendances to the ED following head injury that result in inpatient hospital admission. TBI has become more common in the elderly and if analysis of the proportion of ED attendances that resulted in inpatient admission was stratified by age this would account for age group differences in incidence of injuries .[56] We were unable to differentiate Clinical Decision Unit admissions from other types of inpatient admissions in our data. However, the extent to which Clinical Decision Unit admissions in the UK represent materially different and more cost-effective care compared to other types of hospital admissions and should be treated differently is debatable.[57] Furthermore, only 6 hospitals in Scotland had Clinical Decision Units during the time period of our study and were not established at the same time as the policies considered here.[58]

There is evidence that deaths from severe TBI fell following the introduction of the NICE guidelines.[23] We may have missed this effect due to the undifferentiated cohort of TBI patients used to assess deaths and the use of all-cause mortality. We also could not adjust mortality by age or injury severity.

Estimates of the impact of guidelines will depend on the extent to which the guidelines have been implemented. There are no national audit data on this, though one local audit

conducted in 2001 indicated less than half of patients the SIGN guidelines deemed were safe for discharge from the ED were actually discharged.[25] Our study may therefore underestimate the potential impact of full implementation.

Comparison to previous literature:

A study that assessed the NICE head injury guideline's impact using English data (although not using an interrupted time series) found that increased CT imaging led to an increase in hospital admissions, contrary to expectations.[18] Increased admissions following the introduction of the NICE guidelines could be due to increased diagnosis of TBI due to more CT imaging or the effect of the 4-hour ED target.[18] We found evidence that both factors increased hospital admissions in Scotland.

Analysis of English HES data from 2000-2011 found yearly paediatric hospital admissions for head injury increased from 34 to 37 inpatient admissions per 10 000 children.[59] We found Scottish paediatric admissions fell from 56 per 10 000 children in 1999 to 32 per 10 000 children in 2015. There is evidence that clinicians are less likely to implement head injury guidelines in children.[59-61] A lack of implementation may explain why the SIGN guidelines were not associated with a reduction in paediatric hospital admissions.

Implications:

The overall effect of the SIGN guidelines was to reduce inpatient hospital admissions for head injured patients and this supports previous research indicating early CT imaging may represent a cost-effective management strategy.[16] However, the guidelines were associated with increased inpatient admissions for patients with TBI, possibly resulting from increased imaging identifying more TBI of lower clinical severity. Research better characterising the risk associated with TBI identified by CT imaging could help identify a sub-set of low-risk patients who could be safely discharged from the ED. This could help mitigate the increase in inpatient hospital admissions in this group associated with the SIGN and other similar guidelines.

We found evidence that the 4-hour ED target acted to reverse reductions in hospital admissions in the 16-64 age group associated with the SIGN guidelines. As has been previously argued, performance targets need to be carefully considered before implementation to ensure that they do not have unintended consequences, in this case undermining the benefits of evidence-based clinical guidelines.[62] A more granular approach to the 4-hour ED target that reflects condition specific clinical circumstances, such as the time frame of CT imaging in head injury, could help to prevent such costly unintended consequences.

Given the limitations in the mortality analysis undertaken it is hard to draw conclusions about how effective the SIGN guidelines were at reducing deaths from TBI. Future analysis should attempt to adjust for age and severity of injury and this will require patient level data.

Conclusion:

Increased early CT imaging of head injured patients may reduce hospital admissions. However, this effect may be offset by an increase in the diagnosis of TBI of lower severity and the 4-hour ED target. Future research should aim to better risk stratify patients with TBI identified by CT imaging to help reduce hospital admissions related to increased CT imaging. Care should also be taken when introducing arbitrary performance targets, such as the 4-hour target, to ensure they do not undermine the beneficial effect of clinical guidelines.

Chapter 3: An evaluation of the impact of the NICE head injury guidelines on inpatient mortality from traumatic brain injury: an interrupted time series analysis

Chapter Introduction

This chapter presents the text of a paper published in the BMJ Open in June 2019.[2] The text is identical to that published except for reference, table and figure numbers. Supplementary Material are presented in the thesis appendices and references to these materials have been changed in accordance with this.

Abstract

Objective

To evaluate the impact of National Institute of Health and Care Excellence (NICE) head injury guidelines on deaths and hospital admissions caused by traumatic brain injury (TBI).

Setting

All hospitals in England between 1998-2017.

Participants

Patients admitted to hospital or who died up to 30 days following hospital admission with ICD coding indicating the reason for admission or death was TBI.

Intervention

An interrupted time series analysis was conducted with intervention points when each of the three guidelines was introduced. Analysis was stratified by guideline recommendation specific age groups (0-15, 16-64 and 65+).

Outcome Measures

The monthly population mortality and admission rates for TBI.

Study Design

An interrupted time series analysis using complete Office of National Statistics (ONS) cause of death data linked to Hospital Episode Statistics for inpatient admissions in England.

Results

The monthly TBI mortality and admission rates in the 65+ age group increased from 0.5 to 1.5 and 10 to 30 per 100 000 population respectively. The increasing mortality rate was unaffected by the introduction of any of the guidelines.

The introduction of the 2nd NICE Head Injury guideline was associated with a significant reduction in the monthly TBI mortality rate in the 16-64 age group (-0.005; 95% CI:-0.002 to -0.007).

In the 0-15 age group the TBI mortality rate fell from around 0.05 to 0.01 per 100 000 population, the trend was unaffected by the guidelines.

Conclusion

The introduction of NICE head injury guidelines was associated with reduced admitted TBI mortality rate after specialist care was recommended for severe TBI. The improvement was solely observed in 16-64 year olds.

The cause of the observed increased admission and mortality rates in those 65+ and potential treatments for TBI in this age group require further investigation.

Strengths and Limitations of this study:

This study is the first to use complete national data and the robust quasi-experimental method of interrupted time series analysis to evaluate the impact of the NICE head injury guidelines.

We adjusted our analysis for seasonality, autocorrelation and demographic changes using standard statistical techniques.

Inpatient mortality was assessed at a population level as national data on ED attendance for TBI was unavailable and the guidelines acted to change the admission threshold for TBI identified by CT imaging.

Authors' contributions

I conceived the idea for this study with help from my supervisors Trevor Sheldon, Fiona Lecky and Victoria Allgar and this formed part of my NIHR Doctoral Research Fellowship application. I completed all the analysis. My supervisors Trevor Sheldon and Victoria Allgar provided specialist advice regarding interrupted time series analysis. My supervisor, Fiona Lecky provided specialist advice regarding the clinical context and interpretation of the results. All authors read and approved the final published manuscript.

Background

There are approximately 2.5 million cases of Traumatic Brain Injury (TBI) (injury to the brain/ functional impairment due to external force) annually in the European Union and TBI is a leading cause of death and disability.[3] In higher income countries the epidemiology of TBI has changed from a condition predominantly of younger males resulting from high energy trauma, to older people caused by falls.[8]

One of the important health service challenges is identifying the small proportion of patients with life threatening TBI amongst the large number of patients who attend

Emergency Departments (EDs) following head injury (blunt trauma to the head) and then ensure they receive specialist care, including neurosurgery, within a time critical period.[1] Previous research demonstrated correctly configured emergency health care systems are required to deliver optimal outcomes for patients with severe TBI.[3, 23]

In England, since 2003, three NICE head injury guidelines have been introduced in order to improve the ED identification and subsequent management of TBI (Appendix 1).[1, 12, 13, 63]These would be expected to reduce TBI deaths and unnecessary hospital admissions. All three guidelines advocated increased CT imaging of head injured patients that present with a minimally impaired conscious level equivalent to a Glasgow Coma Scale (GCS) of 13-15. Increased costs from imaging were intended to be offset through reduced hospital admissions.[16] The 2007 guideline additionally recommended that patients with severe TBI should be managed in specialist neuroscience centres. At the time of implementation, concerns were raised that guideline recommendations were based on studies in subgroups and lacked supporting level 1 evidence .[15, 22, 23] Evaluation of the impact of these guidelines on national rates of TBI admissions and patient outcomes, is therefore needed.

We describe the first study to use complete national data and interrupted time series analysis to evaluate the impact of early TBI management guidelines on patient outcomes and admission rates for all severities of TBI.

Methods

Data set:

Hospital Episode Statistics (HES) are collected on all inpatients in England. The Office for National Statistics (ONS) has computerised ICD coding of cause of death information recorded on death certificates.

We used individual patient level HES data provided by NHS Digital on all emergency inpatient hospital admissions in England from April 1998 to April 2017. Reason for admission is recorded using ICD10 coding. For patients with ICD10 diagnostic codes: S00-S09 (indicating TBI) or T04.0 and T06.0 (crushing injury to the head) who died up to 30 days from discharge ONS cause of death was also provided.[18] ONS coding changed from ICD9 to ICD10 in 2001.

Deaths attributable to TBI:

Appendix 14 summarises how deaths attributable to TBI over the study period were identified. 852646 deaths linked to admissions for head injury were identified by NHS Digital. We searched all cause of death fields for ICD9 and ICD10 codes defined by the CDC as indicating a death attributable to TBI (Table 3.1).[64] When any were present the death was coded as attributable to TBI. 34659 deaths attributable to TBI were identified and these were linked to their last recorded admission date as a proxy for when the injury and death occurred. This was not possible for 2862 patients. Neonatal deaths were excluded from analysis due to differences in cause of death coding.

Table 3.1: Annual numbers of deaths and admissions from TBI in England (source NHS digital)

Year	Admissions all age groups	Admissions 0-15	Admissions 16-64	Admissions 65+	Death all age groups	Deaths 0-15	Deaths 16-64	Deaths 65+
*1998	47820	17739	22348	7631	677	45	307	331
1999	63599	23848	29088	10553	964	71	446	453
2000	60001	21774	27793	10280	1076	69	492	525
2001	58497	21065	26553	10774	1105	62	519	532
2002	55941	19579	25808	10424	1178	46	508	634
2003	60336	19630	28405	12239	1294	51	521	729
2004	68662	20361	33298	14937	1342	49	568	734
2005	75391	20417	36832	18093	1484	43	606	840
2006	77333	19696	38005	19566	1570	49	610	917
2007	75219	18128	36473	20566	1665	39	624	1012
2008	74158	17481	34657	21938	1621	26	564	1036
2009	81218	18111	37178	25848	1739	35	603	1105
2010	81032	18008	35064	27856	1817	29	530	1260
2011	82093	18604	33989	29390	1879	35	500	1354
2012	76925	16453	30475	29901	2025	27	525	1474
2013	76429	15966	28983	31379	2204	27	497	1687
2014	79372	15535	28833	34890	2361	15	462	1886
2015	76648	13630	27517	35357	2610	18	493	2102
2016	74242	13120	25228	35488	2682	30	511	2145
*2017	16247	2619	5483	8037	504		79	420

*Data are from April 1998-March 2017, so 1998 and 2017 are part years and small number have been suppressed in accordance with NHS Digital guidance
ICD9 definition TBI: 800, 801, 803, 804, 850, 851, 852, 853, 854, 905.0, 907.0 and 873 ICD10 definition TBI: S01.0–S01.9, S02.0, S02.1, S02.3, S02.7-S02.9, S04.0, S06.0–S06.9, S07.0, S07.1, S07.8, S07.9, S09.7–S09.9, T01.0, T02.0, T04.0, T06.0, T90.1, T90.2, T90.4, T90.5, T90.8 andT90.

Admissions attributable to TBI:

The same ICD10 codes used were used to identify patients admitted with TBI (Table 3.1).[64] We searched the primary diagnostic field in the inpatient HES data set for these codes and when present the reason for admission was coded as due to TBI. Data were cleaned and continuous inpatient spells (CIPS) were created for patients admitted with TBI using the approach outlined by Castelli, Laudicella and Street as this includes transfers within CIPS.[65]

1361537 CIPS for TBI were identified for 1245720 patients. Following cleaning, 402 CIPs were found to have admission dates prior to April 1998 and were excluded. Demographic and comorbidity information was calculated from the first consultant episode of a CIP. This included the monthly proportion of TBI admissions for males, monthly median age of admissions and mean monthly admission Charlson Comorbidity Index Score (using ICD10 code definitions and weights used to calculate the Summary Hospital-level Mortality Indicator (SHMI)).[66] This was compared to adjustment using a modified Charlson Comorbidity Index derived from the national (Trauma Audit and Research Network - TARN) trauma registry.[67]

Outcomes:

The monthly number of patients with deaths and admissions attributable to TBI between April 1998 and March 2017 was calculated. These were stratified into guideline specific age groups: 0-15, 16-64 and65+. Monthly mortality and admission rates were calculated per 100 000 population using Nomis ONS mid-year population estimates for England for each age group.[68]

Statistical Analysis:

A monthly time series of the mortality rate for TBI was plotted for the study period. Interrupted times series analysis (ITS) was conducted assessing the impact of the NICE

guidelines using the ITSA package in STATA 14.[48] ITS analysis is a robust and increasingly used quasi-experimental method for the evaluation of health policies and allows causality to be attributed to an intervention introduced at a specific time point.[38]

The ITS model included three intervention time points corresponding to the introduction of each guidelines in: June 2003, September 2007 and January 2014. Analysis was conducted separately for the 0-15, 16-64 and 65+ age groups. A segmented regression model predicting the mortality rate and hospital admission rate for TBI per 100 000 population in each age group per month was estimated.[38] A discontinuity in the gradient (trend) or intercept (level) of the fitted model was tested for at the time point when each guideline was introduced, and discontinuities in the model were measured in the monthly rate of the outcome per 100 000 population.

To adjust for potential changes in the composition of the TBI population that could possibly affect the risk of mortality a further ITS model predicting the TBI mortality rate adjusted for % male, median age and mean Charlson Comorbidity Index Score of patients admitted with TBI was fitted. Stratification by age group and intervention points were identical to the previous analysis.

In all analyses, autocorrelation of the residuals was assessed using the Durbin-Watson and Rho statistic. Throughout we used the Prais-Winsten transformation adjustment for auto-correlation due to improved fit of the model, deviation from a Durbin Watson statistic of 2 and a non-statistically significant Rho statistic.[38] Seasonality was assessed by introducing a dummy variable to the model in which winter months (December, January and February) were coded 1 and was included in the model when statistically significant.[49] To assess for possible implementation lags a sensitivity analysis was performed for all models in which the 12 months immediately following the introduction of a guideline were removed.[38]

Ethics

This study involved the analysis of anonymised routinely collected data and therefore NHS Research Ethics Committee review was not required. Data were stored and processed in accordance with NHS Digital guidance and data sharing agreement.

Patient and Public Involvement

The Hull and East Yorkshire NHS Trust Trans-Humber Consumer Research Panel and Hull branch of the Headway charity were consulted in the initial stages of developing the research questions addressed in this study. These patient groups highlighted that although national head injury guidelines seemed evidence based, there appeared to be little evidence to show they had achieved their aims.

Results

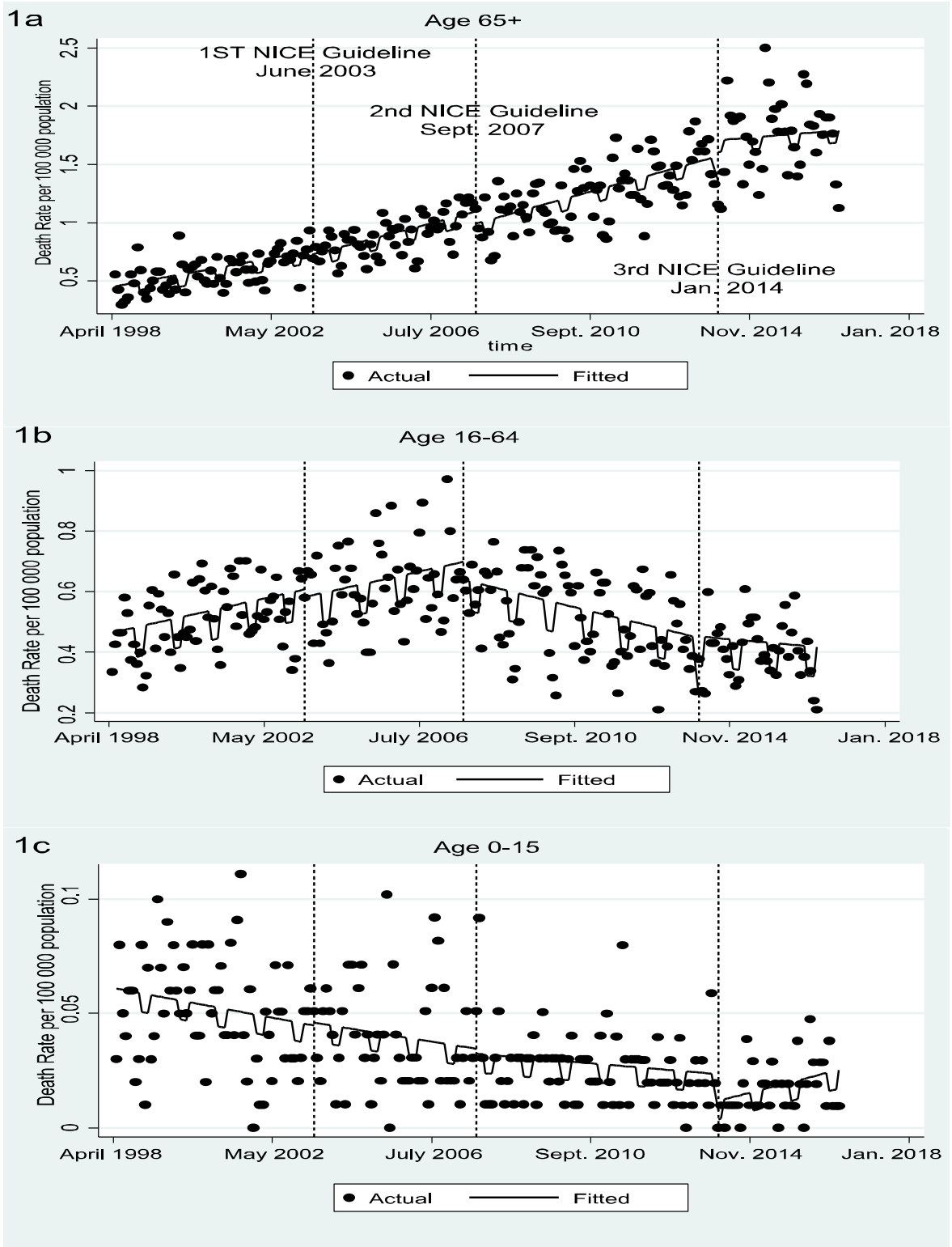
Mortality rate:

Table 3.1 shows the annual number and Appendix 15 shows the annual rates of deaths and hospital admissions for TBI. The proportion of all TBI annual admissions for patients 65+ increased from 17% in 1998 to 48% in 2016 and the proportion of all TBI deaths in this age group increased from 49% to 78% over the same period. Figure 3.1 shows the monthly mortality rate per 100 000 population in each age group. Table 3.2 shows the results of the unadjusted interrupted time series assessing the impact of the NICE head injury guidelines. Deaths were more likely to occur in non-winter months in all age groups and so the figures are seasonally adjusted.

The trends in mortality rate and impact of the guidelines varied between age groups. In the 65+ age group the monthly TBI mortality rate increased from around 0.5 to over 1.5 per 100 000 population over the time period (Figure 3.1a). This was accompanied by an increase in the Charlson score of patients 65+ admitted with TBI (Appendix 16). The NICE

head injury guidelines were not associated with statistically significant changes in the level or trend in the mortality rate (Table 3.2). Subgroup analysis of patients aged 65-84 and 85+ showed that the increase in the mortality rate was greater in those 85+, from around 1 to over 6 per 100 000 population but similar changes were associated with the introduction of the introduction of the guidelines to the whole 65+ population (Appendix 17).

Figure 3.1: The impact of the NICE Head Injury Guidelines on monthly TBI mortality rate per 100 000 population



The 2nd guideline was found to be associated with a large reduction in mortality in the 16-64 age group (Figure 3.1b). Before the guideline, the monthly mortality rate was

increasing but the introduction of the 2nd NICE guideline is associated with a reversal of this trend (-0.005; 95% CI:-0.002 to -0.007) (Table 3.2). The reduction in mortality appears to slow at the time of the introduction of the 3rd NICE guideline but this was not statistically significant. There was an increase in age of patients in the 16-64 age group admitted with TBI but no change in the Charlson comorbidity score over the period (Appendix 16).

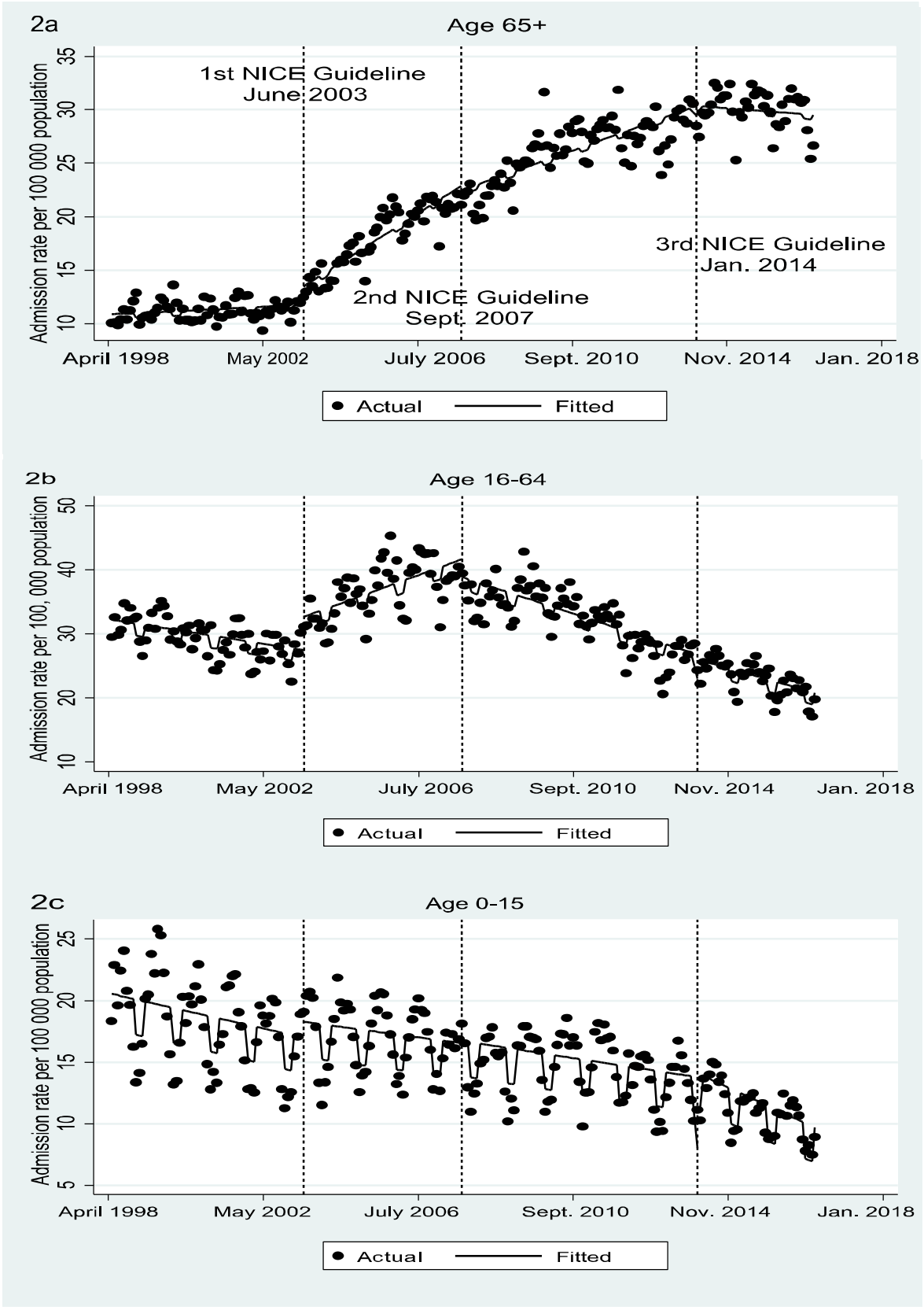
In the 0-15 age group the mortality rate fell continuously over the time period from around 0.05 to 0.01 per 100 000 population (Figure 3.1c). There were fewer monthly numbers of deaths and so more random variability in rates. None of the guidelines were associated with a statistically significant change in the level or trend in the mortality rate (Table 3.2), though the high random variability meant we had lower statistical power to detect such changes as statistically significant.

Adjustment for the monthly median age, mean Charlson Score and proportion of male admissions for TBI did not materially alter the estimates associated with the introduction of guidelines in any of the age groups (Appendix 18). In the 16-64 age group the estimate of the reversal in trend in mortality rate associated with the 2nd Guideline, -0.006 (95% CI:-0.008 to -0.003), was similar to the unadjusted analysis. The levelling off in the rate of reduction in mortality in the 16-64 age group associated with the 3rd NICE guideline became marginally statistically significant, although the estimate is similar, 0.003 (95% CI: 0.00005 to 0.007). No adjustment was made for the standard Charlson score in the paediatric and 16-64 age groups as it did not change over time. The monthly mean trauma modified Charlson score in the 16-64 age group increased slightly from 0 to 1 and adjustment for this increased the estimated size of reversal in mortality trend associated with the 2nd NICE guideline , -0.008 (95% CI:-0.01 to -0.005), (Appendix 16). The sensitivity analysis for the effect of implementation lags did not affect the estimates associated with the introduction of any guideline (Appendix 19).

Admission Rate:

Figure 3.2 shows the trends in monthly TBI admissions stratified by age group and Table 3.3 presents estimates of the change in admission rate associated with the introduction of each Head Injury guideline iteration. The admission rate increased threefold (from around 10 per 100 000 to 30 per 100 000) in the 65+ age group. The introduction of the 1st NICE guideline is associated with large increasing trends in monthly TBI admissions per 100 000 population in both the 65+ age group (0.17: 95% CI: 0.11 to 0.22) and the 16-64 age group (0.25: 95% CI: 0.16 to 0.34) (Table 3.3).[19] The subsequent 2 guidelines are associated with significant reductions in this trend and admission rates level off following the 3rd guideline in the 65+ age group (Table 3.3 and Figure 3.2a). In the 16-64 age group, the TBI admissions trend reverses and declines after the 2nd NICE guideline (-0.33: 95% CI: -0.42 to -0.25) (Table 3.3 and Figure 3.2b).

Figure 3.2: The impact of the NICE Head Injury Guidelines on monthly TBI hospital admissions per 100 000 population



In the 0-15 age group TBI admissions steadily fall over the study period from around 20 per 100 000 to 10 per 100 000 (Figure 3.2c), and is unaffected by the introduction of the guidelines (Table 3.3).

A sensitivity analysis for implementation lags in which the 12 months following the introduction of a guideline were removed from the analysis did not materially change the estimates associated with the introduction of the guidelines in any age group (Appendix 20).

Table 3.2: The impact of the NICE head injury guidelines on monthly TBI mortality rate per 100 000 population

Age Band	**Winter Effect**	**Initial Trend**	**1st NICE Guideline**	**2nd NICE Guideline**	**3rd NICE Guideline**	**Durbin-Watson Statistic**
65+	-0.1 (95% CI: -0.16 to -0.04) P<0.01	0.005 (95% CI: 0.002 to 0.008) P<0.01	**Change level:** -0.034 (95% CI:-0.21 to 0.14) P=0.71	**Change level:** -0.1 (95% CI: -0.27 to 0.07) P=0.24	**Change level:** 0.13 (95% CI:-0.04 to 0.32) P=0.14	Untransformed 1.57 Prais-Winsten 1.86
			Change trend: 0.002 (95% CI:-0.003 to 0.008) P=0.43	**Change trend:** 0.0004 (95% CI: -0.005 to 0.006) P=0.89	**Change trend:** -0.005 (95% CI:-0.01 to 0.002) P=0.14	
16-64	-0.1 (95% CI: -0.13 to -0.06) P<0.01	0.002 (95% CI:0.001 to 0.004) P<0.01	**Change level:** -0.03 (95% CI: -0.11 to 0.06) P=0.57	**Change level:** -0.06 (95% CI:-0.15 to 0.003) P=0.17	**Change level:** 0.005 (95% CI:-0.087 to 0.096) P=0.92	Untransformed 1.79 Prais-Winsten 1.95
			Change trend: -0.00002 (95% CI: -0.003 to 0.003) P=0.99	**Change trend:** *-0.005* *(95% CI:-0.007 to -0.002)* *P<0.01*	**Change trend:** 0.002 (95% CI:-0.002 to 0.005) P=0.38	
0-15	-0.01 (95% CI:-0.01 to -0.003) P<0.01	-0.0003 (95% CI: -0.0005 to -0.00001) P=0.04	**Change level:** 0.001 (95% CI: -0.01 to 0.01) P= 0.18	**Change level:** -0.0021 (95% CI: -0.01 to 0.01) P=0.74	**Change level:** -0.01 (95% CI:-0.03 to 0.002) P=0.09	Untransformed 2.12 Prais-Winsten 1.99
			Change trend: 0.00004 (95% CI:-0.0004 to 0.0004) P=0.17	**Change trend** 0.0001 (95% CI:-0.0003 to 0.0005) P=0.58	**Change trend:** 0.0005 (95% CI: -0.00005 to 0.001) P=0.08	

Table 3.3: The impact of the NICE head injury guidelines on monthly TBI hospital admission rate per 100 000 population

Age Band	Winter Effect	Initial Trend	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline	Durbin-Watson Statistic
65+	-0.44 (95% CI: -0.94 to 0.06) P=0.08	0.01 (95% CI: -0.02 to 0.05) P=0.42	***Change level:*** *1.71* *(95% CI:-0.01 to 3.44)* *P=0.05*	**Change level:** -0.4 (95% CI: -2.08 to 1.27) P=0.64	**Change level:** 0.04 (95% CI:-1.73 to 1.82) P=0.96	Untransformed 1.1 Prais-Winsten 2.09
			Change trend: *0.17* *(95% CI: 0.11 to 0.23)* *P<0.01*	**Change trend:** *-0.08* *(95% CI: -0.13 to -0.03)* *P<0.01*	**Change trend:** *-0.13* *(95% CI:-0.2 to -0.05)* *P<0.01*	
16-64	-1.92 (95% CI: -2.77 to -1.07) P<0.01	-0.08 (95% CI: -0.13 to -0.02) P<0.01	***Change level:*** *5.21* *(95% CI: 2.53 to 7.89)* *P<0.01*	***Change level:*** *-2.76* *(95% CI:-5.35 to -0.16)* *P=0.04*	**Change level:** -0.72 (95% CI: -3.49 to 2.03) P=0.61	Untransformed 1.35 Prais-Winsten 2.11
			Change trend: *0.25* *(95% CI: 0.16 to 0.34)* *P<0.01*	***Change trend:*** *-0.33* *(95% CI: -0.42 to -0.25)* *P<0.01*	**Change trend:** 0.02 (95% CI:-0.09 to 0.13) P=0.73	
0-15	-2.87 (95% CI: -3.40 to -2.34) P<0.01	-0.06 (95% CI:-0.11 to -0.01) P=0.03	**Change level:** 1.3 (95% CI: -1.03 to 3.63) P= 0.27	**Change level:** 0.19 (95% CI: -2.09 to 2.47) P=0.87	**Change level:** 0.34 (95% CI:-2.03 to 2.72) P=0.78	Untransformed 1.07 Prais-Winsten 1.70
			Change trend: 0.02 (95% CI: -0.07 to 0.11) P=0.61	**Change trend** -0.005 (95% CI: -0.08 to 0.08) P=0.91	**Change trend:** -0.08 (95% CI: -0.19 to 0.03) P=0.17	

Discussion

Summary

To our knowledge this is the first study to use national population based data and interrupted time series analysis to evaluate the impact of the NICE head injury guidelines in England. The 2nd NICE guideline was associated with a reduction in the admitted TBI mortality rate in the 16-64 age group at a population level (Table 3.2). We found no other impact on mortality associated with the three guideline iterations.

There was a continual and significant increase in TBI mortality and admission rates in the 65+ age group and a contrasting falling trend in mortality and admission rates in children. (Figure 3.1 and Figure 3.2). Both trends began before the introduction of the NICE guidelines and were not significantly affected by any of the three iterations. In both the 16-64 and 65+ age groups there was a large increase in hospital admissions for TBI at the time the 1st NICE guideline was introduced (Figure 3.2).

Increased imaging was intended to reduce hospital admissions by reducing diagnostic uncertainty but the 1st NICE guideline coincided with the introduction of the 4-hour target.[16 19] We have shown, using Scottish data assessing the impact of similar (SIGN) guidelines (introduced at a different time to the 4-hour target), that the 4-hour target acted to undermine this reduction and cause a large increase in hospital admissions.[34] No mortality benefit was found at the time of the introduction of the 4-hour target in England.

Later guidelines were associated with a reduction in hospital admissions rates in both adult populations assessed (Figure 3.2). Further increases in CT imaging may have reduced hospital admissions, as intended, by reducing diagnostic uncertainty in the ED, without the distorting effect of the 4-hour target introduction.

Strengths:

We used complete national data for England to assess the impact of the NICE head injury guidelines on mortality after admission for TBI at a population level. We have used individual level patient data to define TBI deaths and admissions. We controlled for seasonal factors and auto-correlation using established techniques.[38] We used mid-year population estimates to adjust for changes in the demography of England's population.

Weaknesses

Ideally, we would have estimated the impact of the guidelines on case fatality, as this better measures the impact on the population at risk. The impact on case fatality of those attending ED with TBI could not be estimated because ED data were not collected until 2007. The impact on case fatality of those admitted with TBI could be estimated but because the guidelines resulted in changes in admissions policies and rates, the rate of deaths per admission is difficult to interpret. Instead we analysed the impact on the population TBI mortality rate, as this represents the best available unbiased measure of the guidelines' impact. This outcome may be affected by changes in the underlying population TBI rate that we are unable to account for, although annual attendances to the ED for head injury gradually smoothly increased over the study period (Appendix 21). We were unable to assess possible impact on disability or other patient reported outcomes, as they are not routinely collected.

ONS linked HES data is based on routinely collected administrative data; these can suffer from poor accuracy of injury coding.[53] This is particularly likely in older patients with multimorbidity (TARN – personal communication). Random poor coding, as opposed to a discrete and systematic change in coding practice, however, is unlikely to account for discontinuities observed at the specific time points of interest but may make a discontinuity harder to detect. ONS changed from ICD9 to ICD10 coding of cause of death in 2001. A sensitivity analysis excluding the period that used ICD9 coding did not materially alter the estimate of the reversal in mortality trend associated with the 2nd

guideline in the 16-64 age group. We are unaware of other significant changes to coding practice in the HES or ONS data during the study period.

The limitations of HES data mean that mortality rates could not be adjusted for anatomical severity of brain injury and presenting physiology. However, adjustment for other known predictors of TBI mortality did not materially change estimates associated with the introduction of the guidelines and we are unaware of evidence that the prevalence of these factors changed at the point individual guidelines were introduced.

The impact of guidelines is limited by how well they are implemented. The NICE head injury guidelines have been found to be well implemented, [23] albeit with less compliance to CT imaging recommendations in the paediatric population.[24, 59] There is evidence that each guideline caused step increases in CT head scanning in other age groups, particularly in those 65+.[15, 56]

The reconfiguration of the trauma network in England in 2012 is a co-intervention which could affect the TBI mortality rate.[69] However, we found no impact on mortality associated with the 2014 NICE guideline introduced around this time. Apart from the introduction of the 4-hour ED admissions target in 2004, we are unaware of any other co-interventions that occurred around the time the NICE guidelines were introduced which could account for the observed discontinuities in mortality and hospital admissions.

Comparison to previous literature:

Few previous studies assess the impact of the NICE head injury guidelines (see Table 3.4).[22] A cohort study using Trauma Audit and Research Network (TARN) national registry data suggested the increased rate of transfer of severe TBI patients to neuroscience centres between 2003-2009 was associated with a halving of severe TBI case fatality.[23] TARN data were only collected at approximately half of hospitals in England until 2012 and on a TBI patient subset. Our study, using complete national data and interrupted time series analysis, found that guideline recommended management of patients with severe injuries in specialist centres only reduced the mortality rate in the 16-64 age group.

A paediatric study analysing English HES data from 2000-2011 found a reduction in annual mortality during admissions for head injury after the introduction of 2007 NICE guideline.[59] We found a fall in the mortality rate over the study period in the 0-16 age group which was unaffected by any guideline. This may reflect the greater number of data points we used to estimate the time dependent model and use of interrupted time series analysis to assess for discontinuities. We also used ONS linked HES data to identify deaths directly attributable to TBI up to 30 days following discharge. The observed decreasing mortality and admission rates may reflect improving clinical management or a reduction in TBI in this age group due to improving road traffic safety during the study period. [59]

An economic evaluation of the NICE guidelines found them to be cost effective due to a reduction in hospital admissions predicted from early single centre studies and improved outcomes.[15, 16] A subsequent study using HES data found hospital admissions for head injury increased after the introduction of the 1st NICE guideline.[18] The similar increase in adult TBI admissions we found associated with the 1st NICE guideline probably is due the 4-hour target.[34] We found subsequent NICE guidelines improved outcomes and reduced hospital admissions in the 16-64 but not the 65+ age group, implying the guidelines were less cost-effective in older patients.

Table 3.4: Comparison to previous literature

Previous Study			Current study
	Study population	Findings	Findings
Fuller et al 2009[4]	TARN eligible patients at TARN submitting hospitals (approx. 50% England) between 2003-2009	From the period 2004 onwards as the proportion of patients with TBI transferred and managed in neuroscience centres increased and the risk adjusted mortality rate for TBI fell.	Complete national data for all hospital in England. A reversal in trend in the mortality rate in the 16-64 age group when the 2nd NICE guideline recommending management of patients with severe injuries in specialist centres was introduced.
Marlow et al 2015[24]	Patients aged <16 with ICD10 codes indicating head injury admitted to hospitals in England between 2000 and 2011.	Assessed the annual rate of inpatient deaths (all-cause mortality) for patients admitted with ICD10 codes indicating head injury, Found the death rate fell across the time period, but there was only a statistically significant reduction in the death rate after the 2007 NICE head injury guideline.	The inpatient TBI mortality rate (as indicated by coding of death certificates) for patients aged<16 fell from 1998-2017 and was unaffected by the introduction of the NICE guidelines.
The Trauma and Audit Research Network Report: Major Trauma in Older People[25]	TARN eligible patients at TARN submitting hospitals between 2005 and 2014 (all hospitals in England by 2014)	A large increase in major trauma, including TBI, in patients 65+, disproportionate to UK population demographic changes. Hypothesised due to increased case ascertainment due to more liberal CT imaging.	We found a large increase in the admission rate for TBI in those 65+ from 10 per 100 000 population to 30 per 100 000 population between 2002 and the point the 3rd NICE guideline was introduced in 2014.

Other studies using TARN data have found increases in TBI in patients 65+ disproportionate to population changes and it has been suggested that better case ascertainment due to increased CT imaging in older patients may account for this.[8, 56] The

large increase in admissions for TBI for those 65+ we found at the point the first guideline was introduced, although boosted by the 4-hour target, supports this (Fig 3.2a and Table 3.3). The lack of improvement in admitted TBI mortality in older patients following the 2nd NICE guideline could either result from unequal access to treatment in specialist centres or such treatment appearing to be less effective in this group.

The TARN older persons audit found patients aged over 60 to be less likely to be manged in Major Trauma Centres (where neurosurgical units are located in England) and more likely to experience delays in investigation and be treated by junior staff.[56] However, other studies have found age to be an independent predictor of mortality that is unaffected by early treatment in neuroscience centres.[70, 71]

We are unaware of comparable national evaluations of the impact of head injury guidelines. Evaluations of international Brain Trauma Foundation guidelines, particularly in the USA, have utilised evidence from single centre studies or subsets of patients.[24, 72, 73] Evaluation of their national impact has not been possible due to their variable implementation.[24, 73]

Implications:

We found evidence that only the second NICE head injury guideline was associated with a change in population based TBI mortality. This guideline contained a recommendation for increased management of severe TBI in specialist centres. Much research has focused on determining which head injured patients require CT imaging.[1, 74] Increased diagnosis by itself, however, without a change in subsequent patient management was not associated with improved outcomes in our analysis. Even if apparent increases in TBI rates in older patients reflect the identification of previously unmet need, this still represents a significant health service challenge. Routine ICD coding of TBI is particularly problematic in this group and robust evaluation of treatment in specialist neuroscience centres and other interventions may be required to improve outcomes in older TBI patients. The UK, however, has one of the lowest numbers of ICU beds per population in Europe and when the 2007 guideline recommendation was made concerns were raised about the system

meeting demand.[22, 75] Research needs to focus on how to best configure and ration specialist services for TBI in a transparent and evidenced based way.

Conclusion

This first national evaluation suggests that the introduction of the second NICE head injury guideline was associated with a reduction in the admitted TBI mortality rate in the 16-64 age group and a reduction in TBI admissions in England. The guidelines were not associated with significant changes in the secular trend for TBI admissions and subsequent mortality in children and those aged 65+. Research is needed to identify clinically and cost-effective management approaches for TBI in older patients.

Part 2: Developing a predictive model for deterioration in alert TBI patients with injuries identified by CT imaging.

Introduction:

I have presented evidence in Chapter 2 using national data that an unintended consequence of increased CT imaging recommended by both NICE and SIGN head injury guidelines may be an increase in hospital admissions due to increased radiological diagnosis of TBI.[34] The injuries identified appear to be of lower clinical severity as they are less likely to require neurosurgical intervention. Currently all patients with injuries identified by CT imaging are admitted to hospital for observation in the UK, however, only a small proportion of GCS13-15 patients with injuries on CT require any specific clinical intervention or deteriorate. Accurate prediction of which patients will deteriorate could allow unnecessary admissions to be avoided.

This part of the thesis presents two chapters consisting of word versions of published articles[28, 33] and a further submitted article. Together these chapters address the second research aim of this thesis. Chapter 4 presents a systematic review and meta-analysis of the level of risk of, and risk factors for, deterioration in GCS13-15 patients with injuries on CT. Chapter 5 presents a protocol for the proposed methods of a retrospective cohort study to develop a predictive model for identifying low risk GCS13-15 patients with injuries on CT who could be safely discharged from the ED. Chapter 6 presents the results of this prognostic modelling study.

Method and data sets:

The exact statistical and other methods are presented in detail in the method sections of Chapters 4, 5 and 6. The systematic review was conducted in adherence to international standards.[40] The meta-analysis was completed by pooling of estimates of outcome prevalence, meta regression and pooling of risk factor effect estimates.[76, 77] The design and conduct of the retrospective cohort study was completed in adherence to

international guidelines for the conduct of prognostic research.[78] Composite measures of deterioration encompassing need for hospital admission and other important clinical end points were modelled as binary outcomes using logistic regression to develop parsimonious prediction models which could be used to inform hospital admission and specialist referral decisions.

The data used for the systematic review and meta-analysis were predominantly those reported in the published literature, although individual patient data were provided from a single Italian study.[79] Data for the retrospective cohort study presented in Chapters 5 and 6 were collected at three English hospitals with trauma centres. The ethical and information governance framework in which data collection was completed is presented in the methods sections of these chapters. The retrospective nature of the study meant gaining patient consent to access hospital records was not feasible. Instead, members of the direct care team at each trust accessed retrospective ED and inpatient patient records. As members of the direct care team were accessing routinely collected patient information and clinical data they would have access to as part of their clinical work, patient consent or alternatively Confidentiality Advisory Group (CAG) approval was not required according to UK Health Research Authority guidelines. Patient identifiable study data is currently being stored securely at each NHS trust in accordance with the Health Research Authority approval and will be archived and destroyed at each site in accordance with the study schedule agreed with the Health Research Authority.

Chapter 4: The risk of deterioration in GCS13-15 patients with traumatic brain injury identified by CT imaging . A systematic review and meta-analysis.

Chapter Introduction

This chapter presents the text of a paper published in the Journal of Neurotrauma in March 2018.[28] The text is identical to that published except for reference, table and figure numbers and the use of UK English spelling. Some referencing errors in the published paper have also been corrected and these are follows:

Three references[31, 80, 81] outlining the BIG criteria have been removed from the 3rd sentence of the results section entitled study characteristics (page 79) to leave the 46 references which contributed to the pooled estimates of risk.

The references of the first sentence of the section entitled Neurosurgical Intervention (page 93) in the results section have been corrected to correspond to Figure 4.5.

One of the references for first sentence of the results section entitled progression on repeat CT imaging (page 100) was corrected from Joseph et al 2015[80] to Joseph et al 2015.[27]

The Journal has been informed of these referencing errors.

Supplementary Material is presented in the thesis appendices and references to these materials have been changed in accordance with this.

Abstract

The optimal management of mild traumatic brain injury (TBI) patients with injuries identified by CT brain scan is unclear. Some guidelines recommend hospital admission for an observation period of at least 24 hours. Others argue that selected lower-risk patients can be discharged from the Emergency Department (ED).

The objective was to estimate the risk of death, neurosurgical intervention and clinical deterioration in mild TBI patients with injuries identified by CT brain scan, and assess which patient factors affect the risk of these outcomes.

A systematic review and meta-analysis adhering to PRISMA standards of protocol and reporting. Study selection was performed by 2 independent reviewers. Meta-analysis using a random effects model was undertaken to estimate pooled risks of: clinical deterioration, neurosurgical intervention and death. Meta-regression was used to explore between-study variation in outcome estimates using study population characteristics.

Forty-nine primary studies and 5 reviews were identified that met the inclusion criteria. The estimated pooled risk of the outcomes of interest were: clinical deterioration 11.7% (95% CI: 11.7 to 15.8; neurosurgical intervention 3.5% (95% CI: 2.2 to 4.9%); death 1.4% (95% CI: 0.8% to 2.2%). Twenty-one studies presented within-study estimates of the effect of patient factors. Meta-regression of study characteristics and pooling of within-study estimates of risk factor effect found the following factors significantly affected the risk of adverse outcomes: age; initial GCS; type of injury and anti-coagulation. The generalisability of many studies' was limited due to population selection.

Mild TBI patients with injuries identified by CT brain scan have a small but clinically important risk of serious adverse outcomes. This review has identified several prognostic factors; research is needed to derive and a validate a usable clinical decision rule so that low-risk patients can be safely discharged from the ED.

Keywords: Mild Traumatic Brain Injury; Prognostic modelling; Intra-cranial haemorrhage; Minor Head Injury.

Authors' contributions

I conceived the idea for this study with help from my supervisors Trevor Sheldon, Fiona Lecky and Victoria Allgar and this formed part of my NIHR Doctoral Research Fellowship application. Aditya Borakati acted as a second checker for title and abstract screening and data extraction. I completed all the analysis. My supervisors Trevor Sheldon and Victoria Allgar provided specialist advice regarding systematic review and meta-analysis methods. Fiona Lecky, Will Townend and Andrea Fabbri provided specialist advice regarding the clinical context and interpretation of the results. All authors read and approved the final manuscript.

Background

There are 1.4 million annual attendances in England and Wales to Emergency Departments (EDs) following a head injury (any trauma to the head), and in 2010 2 .5 million people were treated for traumatic brain injury (TBI- injury to the brain or alteration of brain function due to an external force) in the United States.[1] Approximately 95% of patients have an initial Glasgow Coma Scale (GCS) of 13-15, out of a possible 15, indicating normal or mildly impaired responsiveness and orientation.[1, 82] In this large group with head injury and a high conscious level at presentation research has focused on developing decision rules to identify patients who require computed tomography (CT) imaging due to their risk of life threatening traumatic brain injury (TBI).

In the United Kingdom (UK), National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines are used for this risk assessment, based on the Canadian CT head Rule (CCHR).[1,9, 11] Only 1% of head injured patients have life threatening TBI.[1, 9] However, 7% have TBI identified by CT imaging.[83] Most TBI patients who require neurosurgical intervention are identified soon after presentation. The optimal management of the remaining patients in this group remains controversial. A proportion will deteriorate due to the progression of their injuries and so some studies advocate admission to higher dependency levels of care and repeat CT imaging.[29, 84]

Other studies report that some low risk patients may be safely discharged after a short period of observation in the ED.[30, 80] Perel et al have previously outlined how prognostic models can aid clinical decision making in TBI.[85] Subsequent prognostic models, including the IMPACT, TARN and CRASH models, have been useful in predicting adverse outcomes in patients with more severe TBI, but they are not applicable to this patient group .[86-88] Equivalent prognostic models for GCS13-15 patients with CT identified TBI may help safely reduce hospital admissions.

This review is the first to give an overview of the risk of adverse outcomes and prognostic factors in patients with mild TBI (a high or normal conscious level with traumatically

induced brain dysfunction) and injuries identified by CT brain scan. The review specifically:

(i) Estimates the overall risk of adverse outcomes in patients who are initially GCS13-15 in the ED when traumatic brain injury is identified by CT imaging.
(ii) Assesses which prognostic factors affect the risk of deterioration and other clinically important outcomes in this population.

Methods

A systematic review was conducted using the PRISMA P protocol and is reported in accordance with PRISMA guidelines.[89] The review is registered with the PROSPERO prospective register of systematic reviews and the protocol is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051585.

Inclusion Criteria:

Participants

Patients aged ≥12 years with an initial GCS of 13-15 with TBI identified by CT imaging. TBI included any traumatic: extradural haemorrhage, subdural haemorrhage, intra-cerebral haemorrhage, subarachnoid haemorrhage, cerebral contusion, or skull fracture. Studies had to be conducted in the context of an emergency hospital attendance including a presentation to the ED or during admission to an inpatient ward.

Prognostic factors

Factors potentially affecting the risk of adverse outcomes were included in analysis if they were patient factors present at admission including: demographic characteristics, comorbidities, medication use, symptoms, other clinical features or available from initial investigations.

Outcome measures

Primary outcomes: death, neurosurgical intervention or any other measure of clinical deterioration such that admission to hospital was warranted.

Secondary outcome: progression of TBI on repeat CT imaging.

Types of study design

All studies, other than case studies, were included.

Search methods for study identification:

Studies published before 1996 were excluded due to more liberal use of CT imaging to diagnose TBI after this date.[83]

The following electronic databases were searched with results restricted to English language studies:

- EMBASE (via OVID) searched 24/11/2016 1996 to 2016 Week 47
- MEDLINE (R) (via OVID) searched 24/11/2016 1996 to November Week 3 2016
- CINHAL plus (via EBSCO) searched 24/11/2016 1983 to 2016
- Cochrane Central Register of Controlled Trials (CENTRAL); The Cochrane Library 2016 all available dates. Accessed 24/11/2016.

The full search strategy is reported in Appendix 22.

The reference and citation searches of several national guidelines, reports and reviews included: NICE, SIGN and Australian New South Wales (NSW) guidelines, National Institute for Health Research (NIHR) Health Technology Assessment of management strategies for minor head injury, the results of the World Health Organisation (WHO) Collaboration on prognosis in mild traumatic brain injury, systematic reviews assessing prognostic factors in traumatic brain injury, and systematic reviews assessing the utility of repeat CT imaging

in minor head injury. [1, 11, 85, 90-95] All included studies references and citations were searched.

The Trauma Audit and Research Network (TARN) listed publications were searched via the TARN website: https://www.tarn.ac.uk/Content.aspx?ca=9&c=70 (accessed 10/3/2017).

Data Management and Extraction:

Identified studies were stored in EndNote X8 and duplicates removed.

Study Selection

Two reviewers (CM and AB) independently completed title and abstract screening. Full reports of any studies that potentially met the inclusion were selected and assessed. These were screened and studies that did not meet the inclusion criteria were discarded with documented reasons. Disagreements were resolved through discussion or arbitration by a 3rd reviewer (TS).

Data Extraction

The following data were extracted using a pre-piloted data extraction tool: study population and demographics, sample size, outcomes assessed, prognostic factors assessed, whether univariable or multivariable modelling had been undertaken and the overall results of the study. The selection criteria of studies were recorded to assess whether sub-populations with different risk profiles had been studied. The data extracted is presented in Appendix 23.

Assessment of the risk of bias

The Quality in Prognostic Studies (QUIPS) Tool was used to assess the quality of included studies particularly for the risk of bias.[96] Six domains were assessed: study participation; study attrition; prognostic factor measurement; outcome measurement; study confounding; and statistical analysis and reporting.

Data Analysis

Three forms of analysis were undertaken: pooling of adverse outcomes reported in studies, identification of risk factors by exploration of between-study variation in outcomes by study characteristics and a synthesis of common risk factors assessed within studies.

A pooled prevalence of the adverse outcomes of interest and confidence intervals for individual studies were estimated using the Metaprop function (STATA-SE 14).[77] The Freeman-Tukey double arscine transformation was used to include studies with no adverse outcomes and a random effects model was used due to study heterogeneity.[97]

Between-study heterogeneity estimates of outcomes was explored using subgroup analysis. Meta-regression of study characteristics was used to identify factors that affected the risk of the outcomes of interest. Meta-regression of multiple study characteristics' effect on the prevalence of adverse outcomes was assessed using the Metareg function (STATA-SE 14) with weighting incorporating a measure of between study variation (tau2).[76, 98] The log odds of clinical deterioration, neurosurgical intervention and death were assessed as dependent variables and the standard error of the log odds was used to approximate the within study standard error. To account for studies with no outcomes, 0.5 was added to both the outcome estimates and the sample size (consequently, in graphic representations of the meta-regression the estimated risk can only tend towards zero).

Where studies had assessed the effect of risk factors on the outcomes of interest using individual data, analysis was categorised as univariable or multivariable. Univariable meta-analysis of prognostic factor effect estimates reported in primary studies was completed using Review Manager 5.3 where possible.[99] A Random Effects model was used due to the heterogeneity of study populations, prognostic factor and outcome measures.[97] Meta-analysis of multivariable models was not possible due to limited numbers and variation in outcome and prognostic factor measurement.

Results

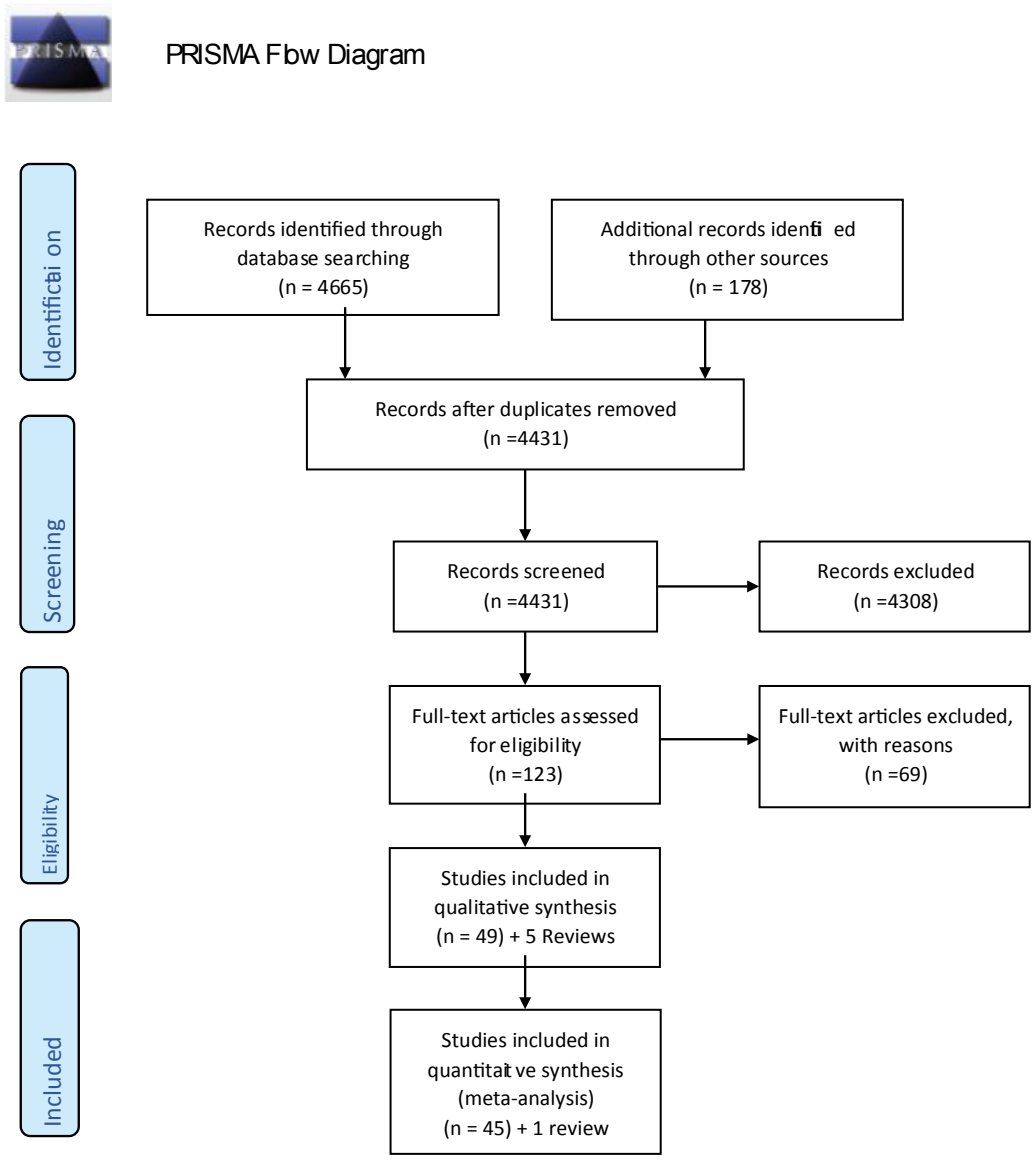
Search Result

The electronic search strategy was completed on the 24/11/2016 and identified 4665 studies. Of these 412 were duplicates, leaving 4253 studies for title and abstract screening (Fig. 4.1). Following title and abstract screening 69 studies[27, 80, 81, 84, 100-164] and 2 reviews[94, 95] were retrieved. A "grey" literature search identified a further 129 studies for title and abstract screening of which 3 were retrieved.[8, 165, 166]

Reference and citation searching of included studies and selected reviews and guidelines identified another 46 studies[29-31, 79, 111, 167-207] for full retrieval and 3 additional systematic reviews[92, 93, 208] for reference and citation searches.

In total 118 primary studies and 5 systematic reviews were retrieved.

Figure 4.1: PRISMA flow-diagram showing selection of studies for inclusion in the systematic review



Study Selection

Forty-nine primary studies met the inclusion criteria. [27, 29-31, 79-81, 84, 100, 102, 104, 109, 113, 114, 124, 126, 128, 130, 131, 133, 134, 136, 137, 140, 142, 144-149, 157, 158, 161, 164, 167-174, 176-178, 183, 194, 199] One review presented new study data.[93] The 4 remaining reviews formed part of the narrative synthesis. [92, 94, 95, 208] The reasons for excluding the remaining 69 studies are presented in Appendix material 24. Anonymised individual patient data were provided by the authors of a cohort study to allow outcomes for initial GCS13-15 patients to be calculated, so this study is included.[79]

Study Characteristics

Appendix 25 presents the characteristics of included studies. Seven prospective studies were identified[79, 100, 137, 145, 146, 161, 183] and 4 studies had a sample size of over 1000.[134, 158, 168, 178] Forty-six studies estimated the outcomes of interest and contribute to pooled estimates of risk.[27, 29, 30, 79, 84, 100, 102, 104, 109, 113, 114, 124, 126, 128, 130, 131, 133, 134, 136, 137, 140, 142, 144-149, 157, 158, 161, 164, 167-174, 176-178, 183, 194, 199] Four studies present data regarding specific injury sub-types.[104, 126, 142, 173] One study only contributes to the narrative synthesis due to the outcome measure it assessed.[114] Three studies present the Brain Injury Guidelines (BIG) risk stratification tool.[31, 80, 81] As this tool was applied to all TBI patients and initial GCS forms part of risk stratification, these studies contributed to the narrative synthesis.

Twenty-one studies present either univariate or multivariable analysis assessing prognostic factors' effect on the outcomes of interest.[27, 79, 84, 109, 113, 126, 137, 140, 142, 144-149, 158, 168-171, 199] Sixteen studies present multi-variable models using logistic regression or recursive partitioning.[27, 84, 109, 113, 126, 137, 140, 142, 144, 145, 148, 149, 168, 170, 171, 199] Only 2 studies attempted to validate such models by splitting the study data sets.[137, 168]

Quality Assessment

QUIPS quality scores are presented in Appendix 23.[96] The following common methodological issues were identified.

Study recruitment was often not representative of all GCS 13-15 patients with TBI identified by CT imaging. Sixteen studies that contribute to the pooled estimates of adverse outcomes only included patients that had undergone repeat CT imaging and so are likely to represent a higher risk population.[27, 29, 93, 145-149, 157, 161, 172, 174, 176, 177, 194, 199] Even when re-imaging was presented as routine practice, it was often indicated that not all patients were re-imaged and included in analysis.[84] Many other studies excluded higher risk anti-coagulated patients or those with more severe injuries.

Prognostic factor measurement was not consistent. Continuous variables were dichotomised at different thresholds or the same risk factor was measured with different methods. For example, the severity of injury identified by CT imaging was assessed with 10 different measures. Most studies were retrospective and reliant on the accuracy of case notes and radiological reports. The small sample size of many studies prevented multivariable modelling with all variables identified in univariable modelling as affecting deterioration.[109]

In 32 studies outcomes were assessed during inpatient admission and so patients who were discharged and deteriorated were missed. In other studies, is wasn't clear when outcome measures were assessed. Eight different measures of clinical deterioration were used in 18 studies.

Several studies included patients with extra-cranial injuries and significant comorbidities. Extra-cranial injuries caused clinical interventions, and in studies that measured deterioration in this way this was a potential source of bias.[137] Other studies indicated some recorded deaths were related to comorbidities instead of TBI.[113, 144]

Risk of Adverse Outcomes and Exploration of Between-Study Variation

Death

Twenty-seven studies assessed the outcome of death. [30, 79, 84, 100, 113, 124, 128, 131, 133, 134, 136, 140, 144-146, 149, 157, 164, 167, 169-172, 174, 183, 194, 199] The estimated risk of death for these studies ranged between 0 and 6% (median 1.1%), and with a pooled prevalence of 1.4% (95% CI: 0.8% to 2.2%) (Fig. 4.2). Studies that selected only initial GCS15 patients had a pooled estimate of mortality of 0.03% (95% CI: 0 to 0.28%). Studies that selected populations for non-ICU admission or other conservative care pathways had an estimated prevalence of death of 0.1% (95% CI: 0 to 0.6%).

The effect on mortality of mean GCS, average age and selection of study population for a lower level of care was explored using meta-regression. Increased age of study population was associated with a higher risk of death (1.05 95% CI: 1.00 to 1.12) (Fig. 4.3). Whilst higher study population GCS was associated with a lower risk of death (0.12 95% CI: 0.02-0.86) (Fig. 4.4). The percentage of patients taking anticoagulants in studies was not associated with the prevalence of death (1.05 95% CI: 0.95-1.17), but selection for a lower level of care compared to a higher level of care was (0.27 95%C.I. 0.08-0.94). When average age of the study population and mean study GCS were assessed in a multivariable model they remained statistically significant predictors of mortality (Table 4.1), with an adjusted R squared of 38%, indicating that these 2 factors explained over a third of the variation in study estimates.

Figure 4.2: Risk of Death stratified by initial GCS

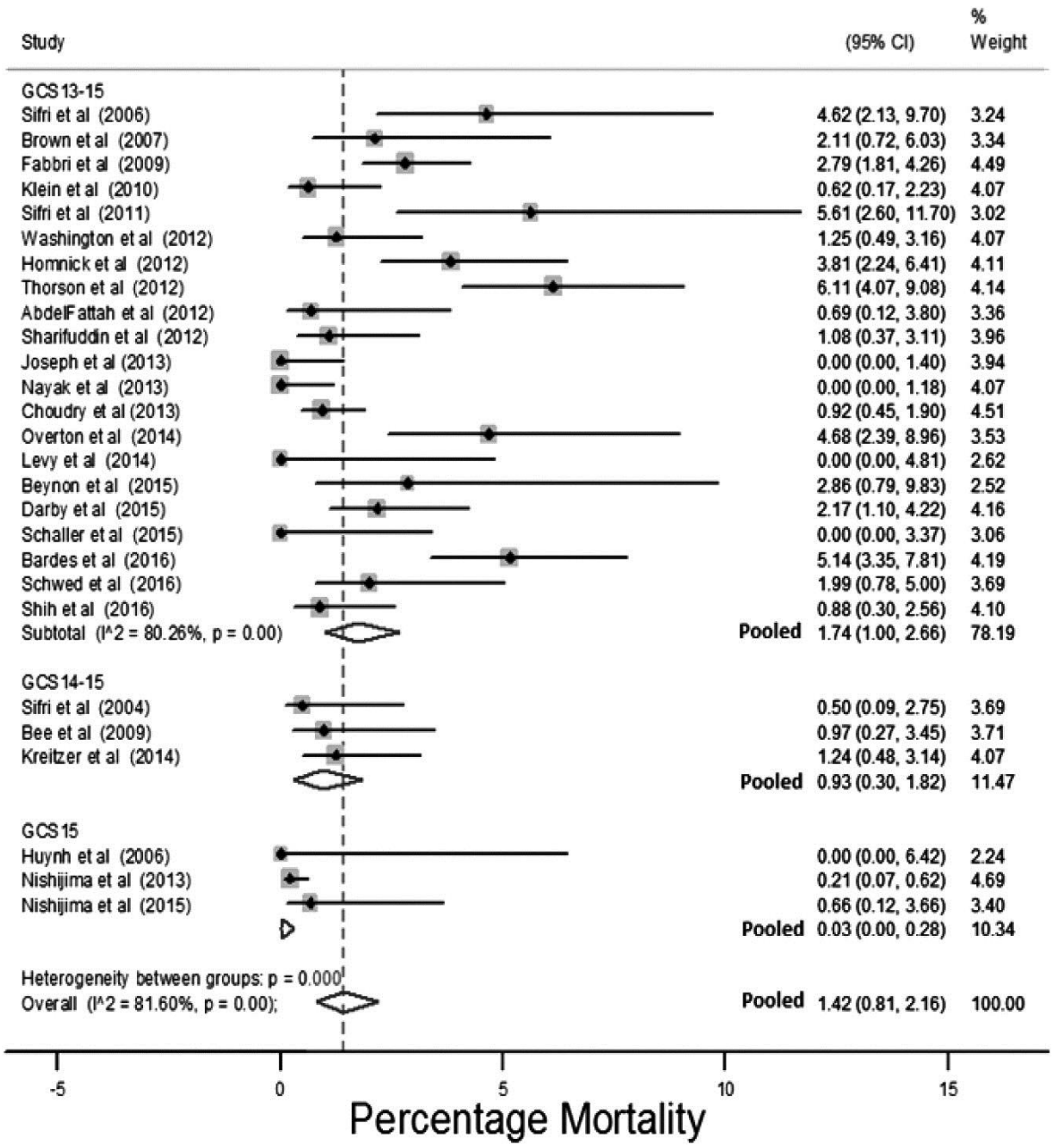


Figure 4.3: Meta-regression risk of death by mean age study population (Coefficient meta-regression1.05 (95% CI: 1.00 to 1.12 P=0.049)

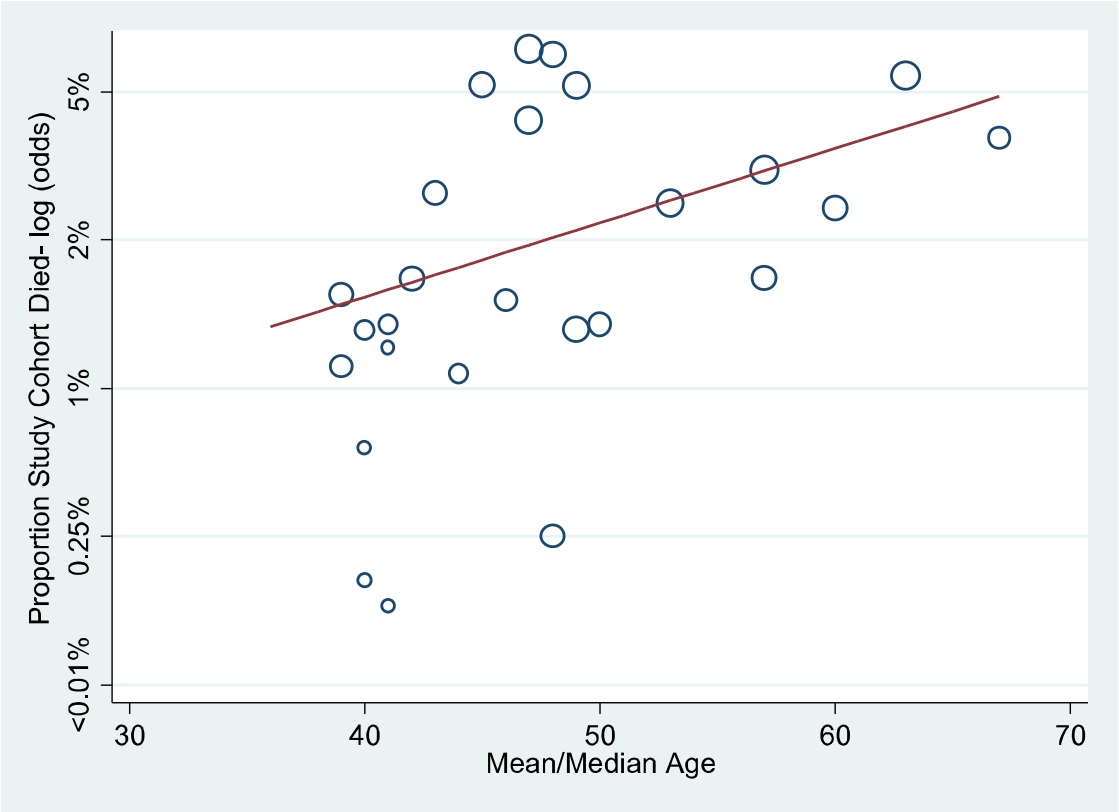


Figure 4.4: Meta-regression risk of death by mean study population GCS (Coefficient meta-regression (0.12 95% CI: 0.02-0.86 P=0.04)

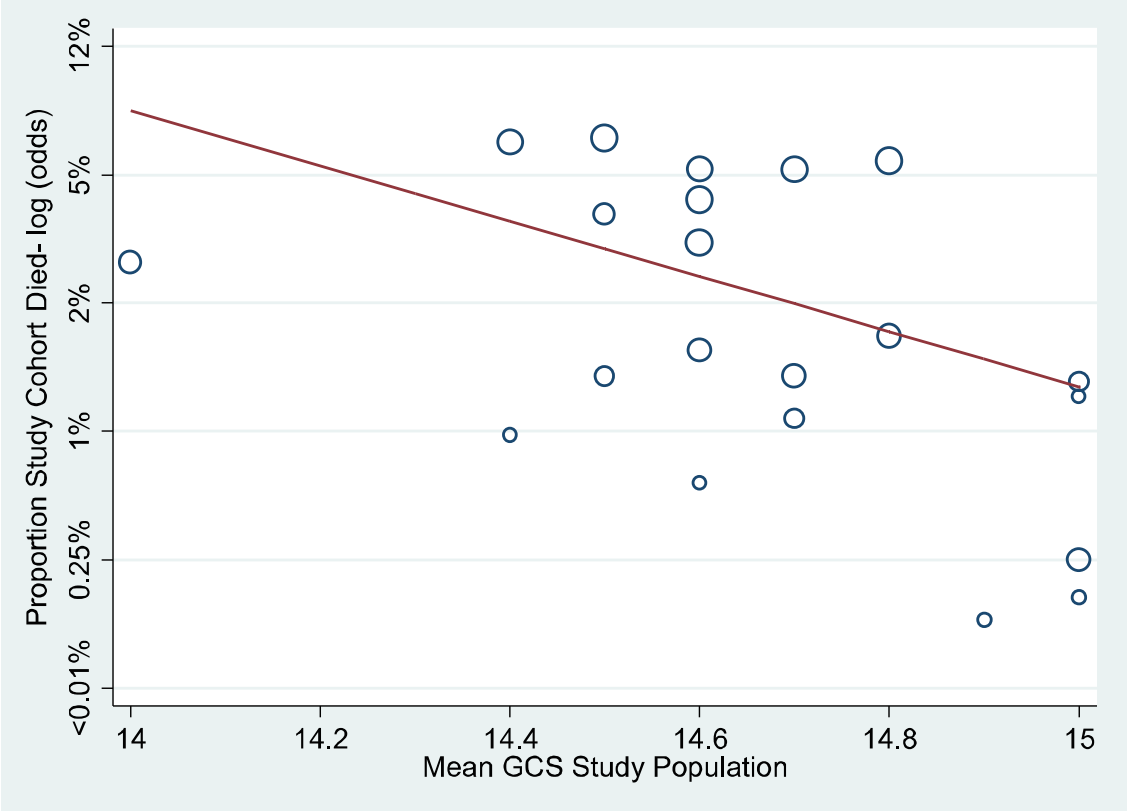


Table 4.1: Meta regression of study factors predictive of death, neurosurgery and clinical deterioration

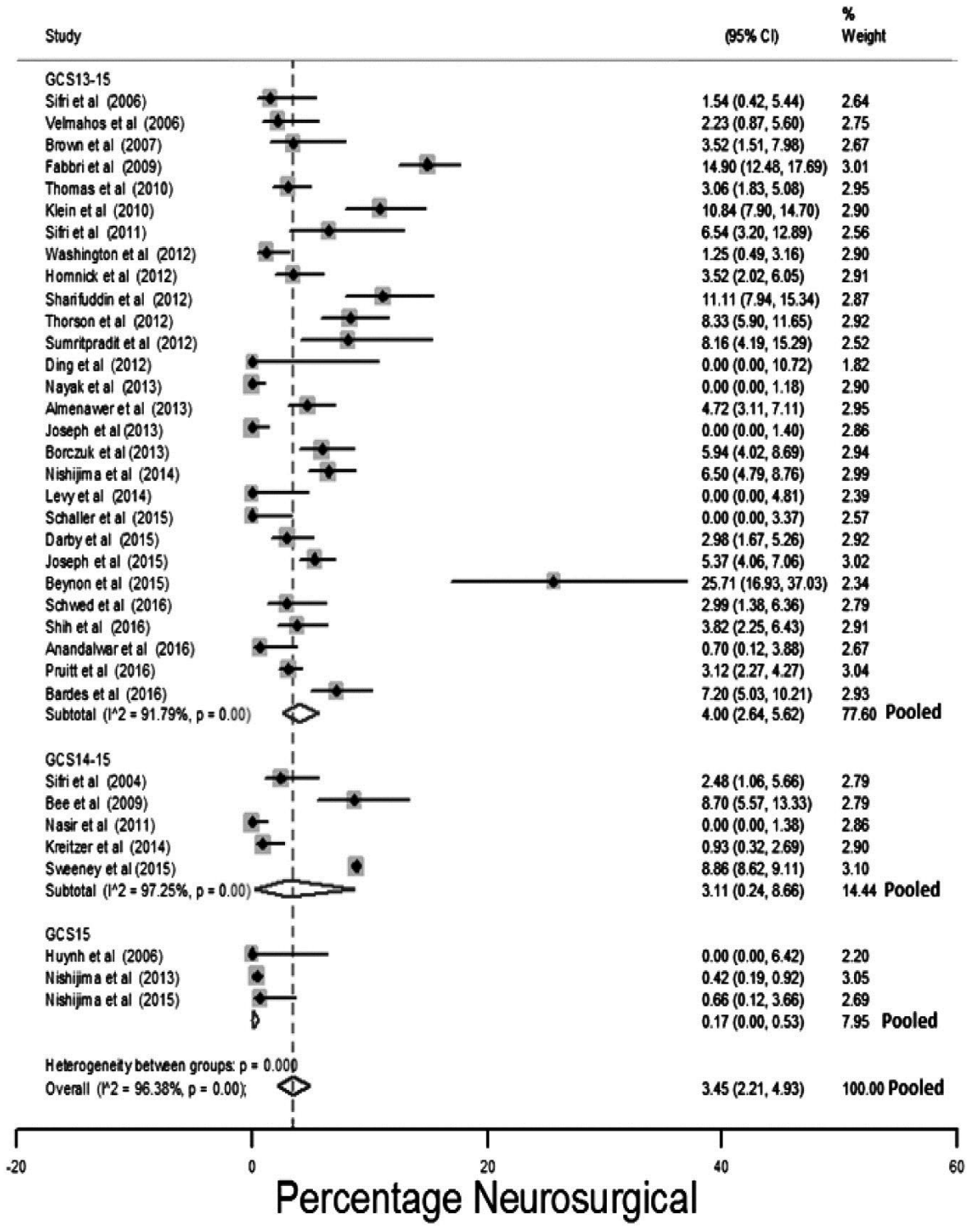
Factor	Outcome	Unit Increase Affect Odds Univariable Model	Unit Increase Affect Odds Multivariable Model
Mean Age Study Population	Death	1.05 (95% C.I. 1.0003-1.12) P= 0.049	1.06 (95% C.I. 1.0002-1.12) P= 0.049
Mean GCS Study Population	Death	0.12 (95% C.I. 0.02-0.86) P=0.04	0.09 (95% C.I. 0.01- 0.59) P=0.02
Lower risk study population versus ICU population	Death	0.27 (95% C.I. 0.08-0.94) P=0.04	
Unselected study population versus ICU population	Death	0.81 (95% C.I. 0.22-1.97) P=0.63	
Percentage population Anticoagulated	Death	1.05 (95% C.I. 0.95-1.17) P=0.32	
Mean Age Study Population	Neurosurgery	1.01 (95% C.I. 1.02-1.11) P=0.01	1.09 (95% C.I. 1.02-1.16) P=0.02
Mean GCS Study Population	Neurosurgery	0.71 (95% 0.01- 0.56) P=0.01	0.12 (95% C.I. 0.02- 0.91) P=0.04
Lower risk study population versus ICU population	Neurosurgery	0.13 (95% C.I. 0.04-0.41) P<0.01	0.67 (95% C.I. 0.10- 4.37) P=0.66
Unselected study population versus ICU population	Neurosurgery	0.95 (95% C.I. 0.43-2.12) P=0.90	1.34 (95% C.I. 0.45-4.02) P=0.58
Percentage population Anticoagulated	Neurosurgery	1.1 (95% C.I. 1.01-1.19) P=0.04	
Exclusion of anti-coagulated patients in study selection	Neurosurgery	0.63 (95% C.I. 0.27-1.43) P=0.26	1.33 (95% C.I. 0.51- 3.49) P=0.54
Mean Age Study Population	Clinical Deterioration	1.01 (95% C.I. 0.95-1.09) P=0.64	1.02 (95% C.I. 0.93-1.12) P=0.59
Mean GCS Study Population	Clinical Deterioration	0.36 (95% C.I. 0.04-3.20) P=0.33	0.26 (95% C.I. 0.02-3.76) P=0.29

Neurosurgical intervention

Thirty-six studies reported neurosurgical outcomes.[27, 29, 30, 79, 84, 93, 102, 109, 124, 128, 131, 133, 134, 136, 137, 144-149, 157, 161, 164, 167-172, 174, 176, 178, 183, 194, 199] Figure 4.5 presents the estimates of the proportion of patients that underwent a neurosurgical procedure stratified by the GCS

inclusion criteria. Reported neurosurgical intervention prevalence ranged between 0 and 26% (median 3.1%). The high proportion requiring neurosurgical intervention reported by Beynon et al[164] may reflect the greater use of anticoagulants or anti-platelets (33/70 participants).

Figure 4.5: Risk of neurosurgery stratified by the initial GCS of the study population



The pooled estimated neurosurgical intervention risk was 3.5% (95% CI: 2.2 to 4.9%). An I^2 of 96.4% indicated considerable heterogeneity. Studies conducted on initial GCS 15 patients had a lower prevalence of neurosurgical intervention: 0.2% (95% CI: 0 to 0.5%). Sensitivity analysis of selection of the study population for reduced care, such as discharge, a non-ICU admission or non-routine repeat CT imaging found the pooled estimate of neurosurgical intervention in these studies to be 0.1% (95% CI: 0 to 0.5%).

The of result of meta-regression using: mean study population GCS, mean study population age, anticoagulation and selection of study population for non-ICU admission or other reduced care pathways is shown in Figures 4.6, 4.7, 4.8 and Table 4.1. Increasing age (1.01 95% CI: 1.02 to 1.11) and increasing percentage of study population taking anti-coagulants (1.1 95% CI: 1.01 to 1.19) was associated with a higher risk, whilst an increasing GCS (0.71 95% CI:0.01 to 0.56) was associated with a lower risk, of neurosurgical intervention.

Fig. 4.7 shows a cluster of 4 small studies with low mean ages that appear to have a disproportionately low estimated prevalence of neurosurgical intervention.[30, 124, 133, 176] This is explained by: exclusion of anti-coagulated patients,[30, 124, 133] selection of patients for non-ICU admission or other reduced other care pathays,[30, 124, 133] and exclusion of patients with large injuries[30].

When the effect of population selection for reduced clinical management, exclusion of anticoagulated patients (only 23/36 studies reported percentage of anti-coagulated patients), mean age and GCS of the study population were all included in a meta regression, age and GCS were the only statistically significant predictors of neurosurgical intervention (Table 4.1). The adjusted R squared of the model was 48%, indicating that these factors accounted for almost half of between study variation.

Clinical Deterioration

Eighteen studies measured prevalence of clinical deterioration.[30, 109, 113, 134, 137, 140, 144, 145, 147-149, 170, 171, 174, 177, 178, 183, 194] The estimated risk of deterioration ranged between 0 and 24.5% (median 12.8%). Figure 4.9 presents study estimates of the percentage of patients that deteriorated, with 95% confidence intervals and stratified by how the outcome was assessed. A pooled prevalence of 11.7% (95% CI: 8.21 to 15.8%) for some form of clinical deterioration was estimated with an I^2 of 95.7%.

Estimates were stratified by: initial GCS of patients, whether the included population were all selected for repeat CT imaging, the inclusion of anticoagulated patients, the follow up period and exclusion of patients with extra-cranial injuries. None of these factors reduced the observed between study heterogeneity.

The effect of: mean GCS study population, mean age study population, study population selection, exclusion of patients with extracranial injuries, and exclusion of anti-coagulated patients was explored using meta-regression. As only 18 studies measured this outcome the model was restricted to 2 variables. No factor assessed individually or in conjunction with another factor was found to statistically affect the risk of clinical deterioration. Higher age and lower GCS were non-statistically associated with a higher risk of clinical deterioration (Table 4.1).

Figure 4.6: Meta-regression of risk of neurosurgery by mean GCS study population (Coefficient odds 0.71 (95% 0.01- 0.56) P=0.01)

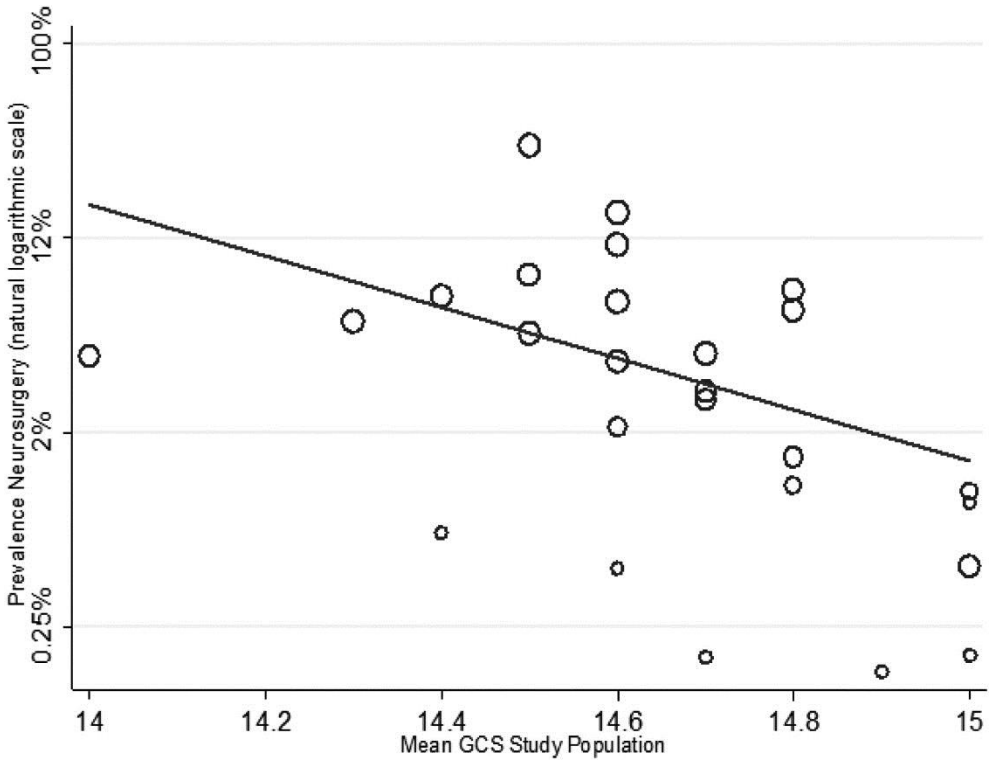


Figure 4.7: Meta-regression of risk of neurosurgery by mean age study population (Coefficient odds 1.01 (95% C.I. 1.02- 1.11) p=0.01)

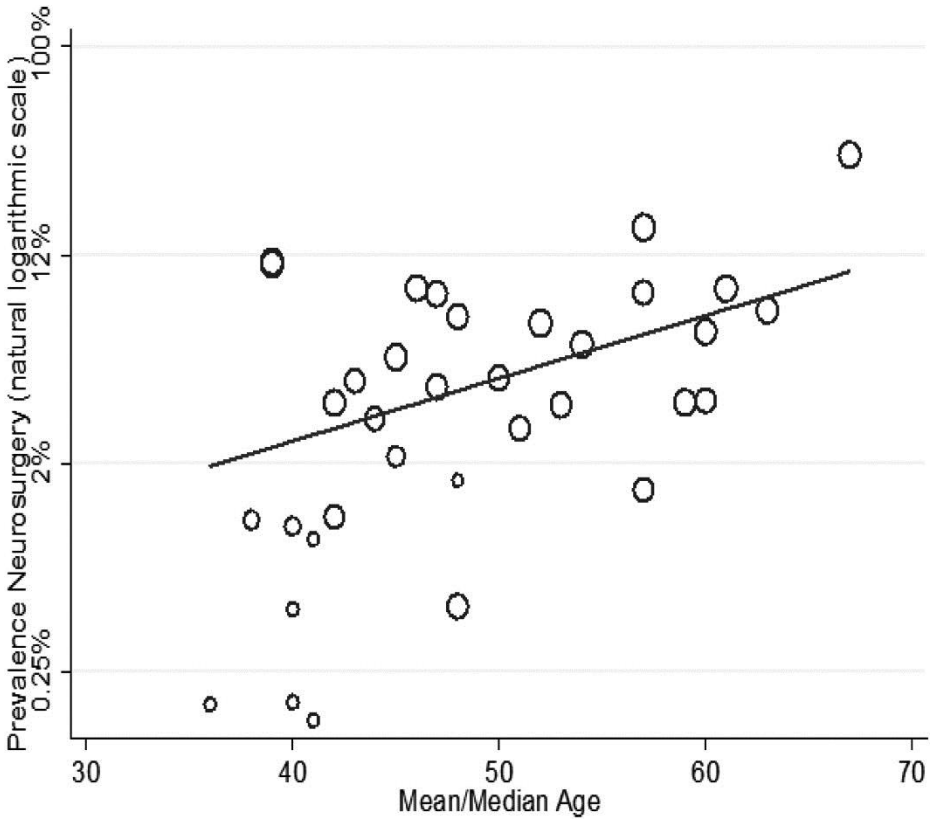


Figure 4.8: Meta-regression of risk of neurosurgery by percentage of study population taking anti-coagulants (Coefficient odds 1.1 (95% C.I. 1.01-1.19) p=0.04)

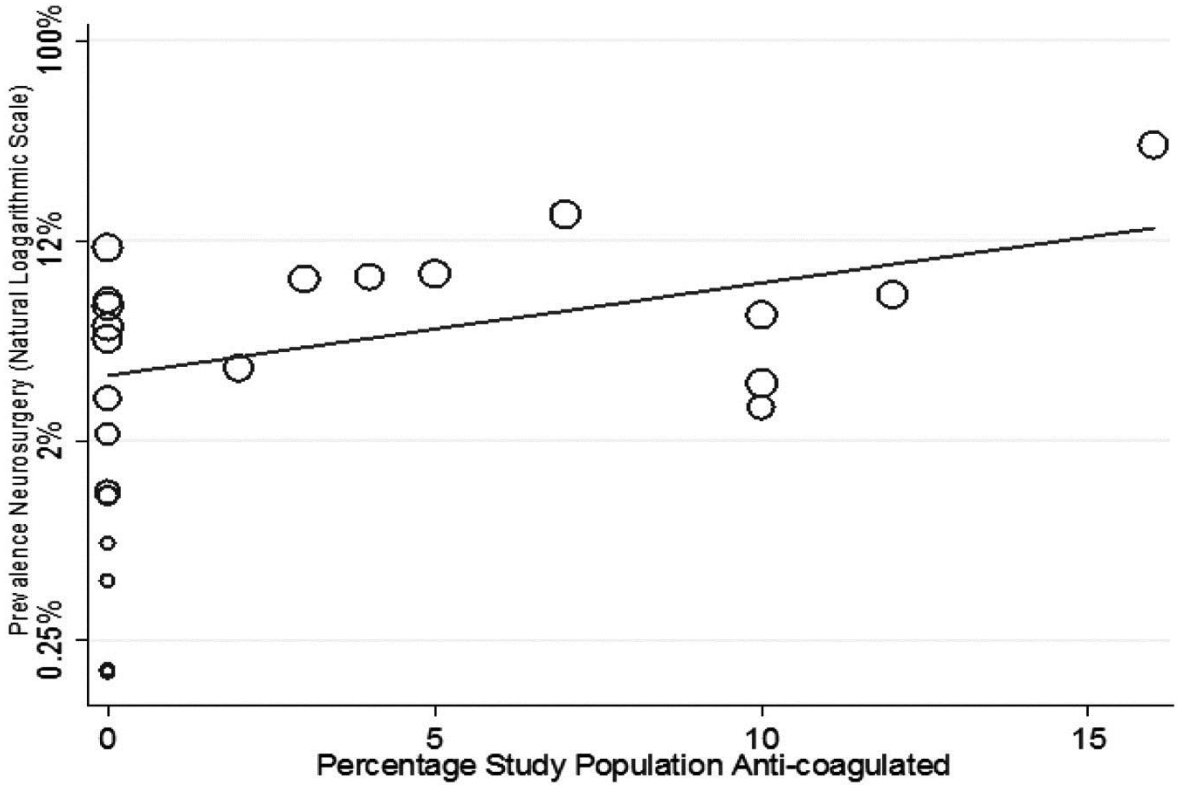
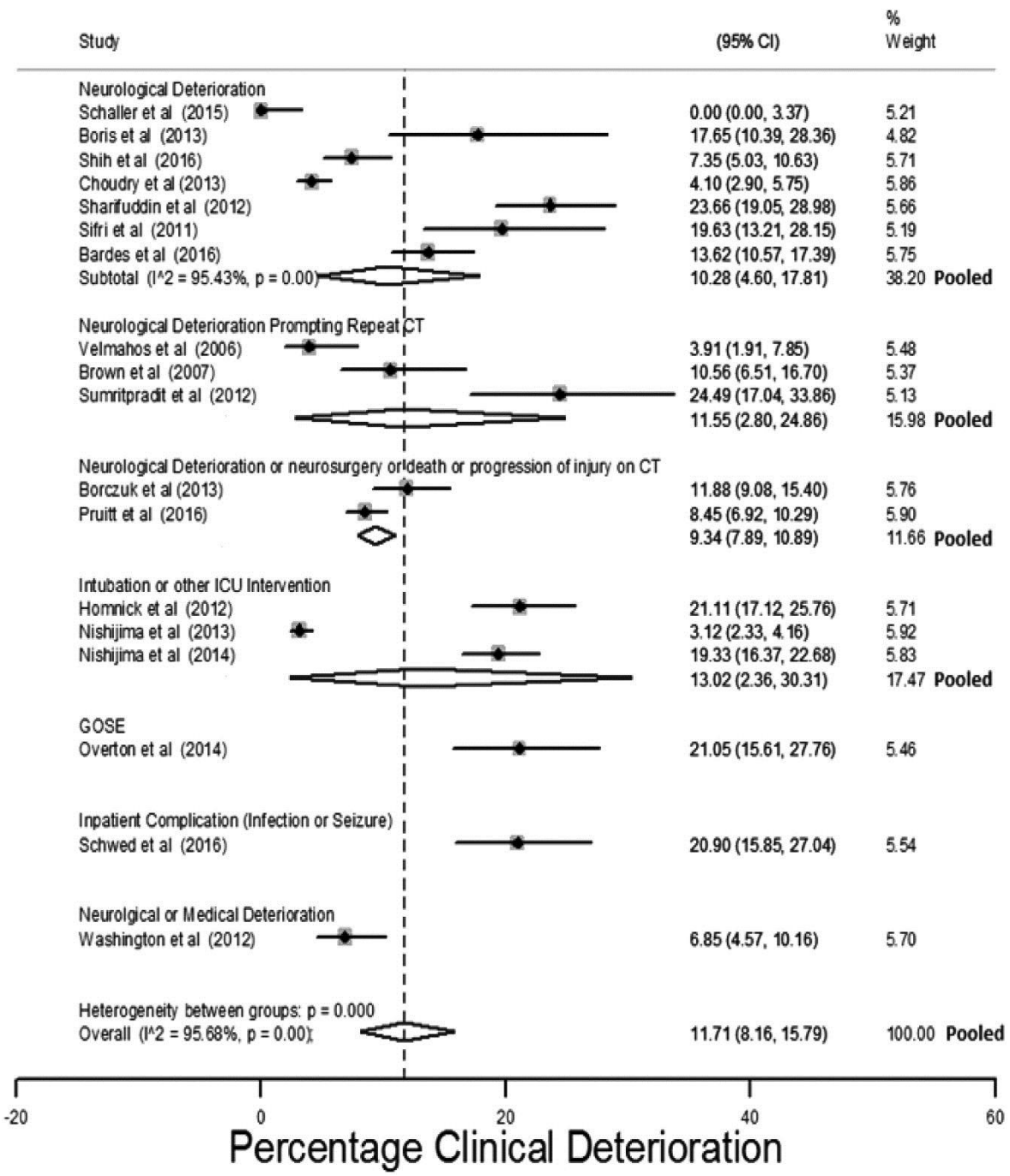


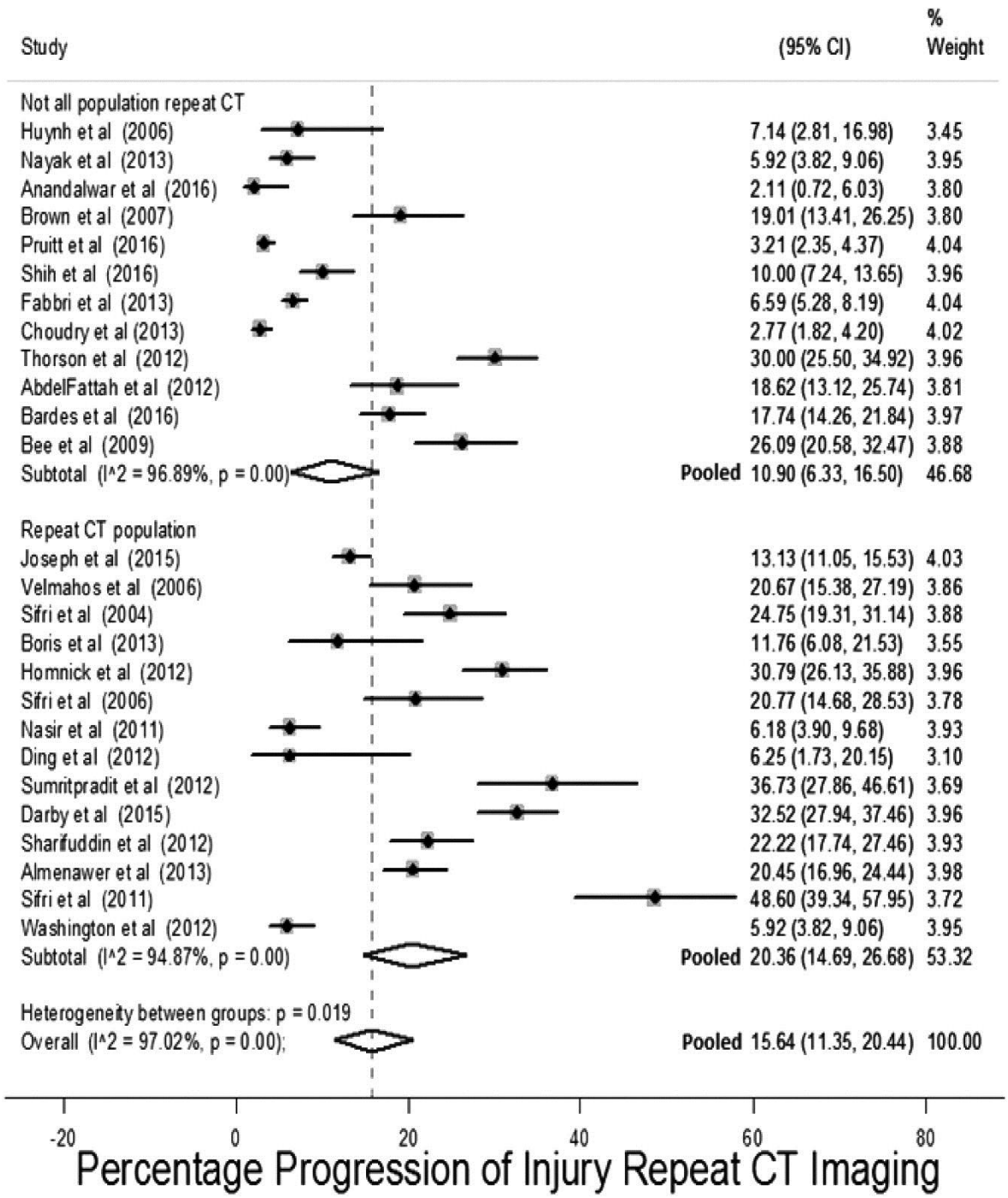
Figure 4.9: Estimates of clinical deterioration stratified by the outcome measure



Progression Repeat CT imaging:

Twenty-six studies assessed the outcome progression of the initial injury on repeat CT imaging. [27, 84, 93, 100, 102, 113, 133, 145-149, 158, 161, 167, 169-172, 174, 176-178, 183, 194, 199] The prevalence of this outcome in these studies is presented in Figure 4.10, stratified by whether studies only included patients that had undergone repeat CT imaging. The pooled estimate for this outcome was 15.6% (95% CI: 11.3 to 20.4%). There is a high degree of heterogeneity with a range in risk of progression between 2% and 48% (median 36.5%) and I^2=97%. The non-statistically significant higher pooled risk in studies that included only patients that had undergone repeat CT imaging probably reflects selection of higher risk patients to repeat imaging. Subgroup analysis of study characteristics did not find any factors that accounted for the heterogeneity. This is probably the result of different criteria used to triage patients to repeat CT imaging and definition of progression of injury.

Figure 4.10: Risk on repeat CT imaging of progression of injury stratified by whether entire population selected for repeat imaging



Prognostic Factors Assessed in Primary Studies

Twenty-one studies presented within study estimates of effect of individual risk factors on the outcomes of interest (Appendix 25) and the factors assessed are presented in Appendix 26.[27, 79, 84, 109, 113, 126, 137, 140, 142, 144-149, 158, 168-171, 199] The most influential factors were: age; initial GCS; severity of CT finding; type of injury; anti-coagulation; and anti-platelet medication (Table 4.2). Individual forest plots are presented in Appendix 27.

Table 4.2: Summary of effect estimates of risk factors assessed within studies

Risk Factor	Number of Studies Assessed in	Pooled Univariable Effect*	Effect Multi-variable Models**	Likely Effect on Risk
Age	18[27, 84, 109, 113, 126, 137, 140, 142, 144, 145, 147-149, 168-171, 199]		+6/11	+
Initial GCS 15	7[109, 113, 137, 144, 145, 148, 171]	OR 0.35 95% CI: 0.23 to 0.52	- 4/4	-
Severity CT brain	9[27, 84, 113, 126, 137, 144, 147, 149, 170]		+7/8	+
Isolated SAH	5[109, 144, 148, 168, 178]	OR 0.19 95% CI: 0.07 to 0.5	-1/2	-
Isolated EDH	5[109, 144, 148, 168, 178]	OR 2.26 95% CI: 1.9 to 2.68	+1/1	+
Isolated SDH	5[109, 144, 148, 168, 178]	OR 1.82 95% CI: 0.69 to 4.77	+2/2	
Isolated Contusion	3[109, 168, 178]	OR 0.24 95% CI: 0.2-0.28	0/1	
Anti-coagulation	12[79, 84, 109, 113, 126, 145, 147-149, 168, 170, 171]	OR 1.45 95% CI: 1.28-1.64	0/2	+
Aspirin	6[109, 126, 137, 147, 158, 171]	OR 1.30 95% CI: 0.95-1.78		
Clopidogrel	6[109, 126, 137, 147, 158, 171]	OR 1.79 95% CI:1.17-2.72		+

*Pooled estimate of effect on risk of neurosurgery or clinical deterioration

**Indicates number of multivariable models where factor was found to be a significant predictor and direction of effect on risk

Age

Age was evaluated as a factor in prognostic modelling in 18 primary studies.[27, 84, 109, 113, 126, 137, 140, 142, 144, 145, 147-149, 168-171, 199] Ten studies[27, 109, 113, 137, 144, 145, 147-149, 171] assessed age

using 4 different dichotomous cut offs and 11 studies measured age as a continuous factor. [84, 126, 140, 142, 144, 147, 148, 168-170, 199] Multivariable models included: logistic regression with age either a dichotomised or continuous variable, or decision tree analysis.

Of these 18 studies: six assessed the outcome of clinical deterioration; 8 assessed the outcome of neurosurgical intervention; 1 measured death as an outcome; and 8 studies evaluated progression of injury on repeat CT imaging. Despite being the most commonly assessed prognostic factor, due to the variation in measurement and the outcomes assessed, it was not possible to undertake a pooled analysis.

Increased age was associated with an adverse outcome in 9 of the 19 univariable models presented. Age was a significant predictor of an adverse outcome in 2 of 5 multivariable models where it was treated as a continuous variable.[140, 142, 168, 199] However, in 4 of 6 multivariable models where it was dichotomised, older age predicted the outcomes of interest. [27, 113, 137, 144, 149, 171] This may indicate a non-linear relationship with older age groups having a disproportionately higher associated risk of adverse outcomes.

Initial GCS

Twelve primary studies presented within study estimates of the effect of initial GCS on the risk of the outcomes of interest.[84, 109, 113, 126, 137, 140, 144, 145, 148, 168, 170, 171] Univariable effect estimates of initial GCS 15 were pooled for studies assessing clinical deterioration and neurosurgical intervention as an outcome with individual patient data provided by Fabbri et al and an initial GCS=15 was protective against clinical deterioration or neurosurgical intervention (pooled OR 0.35 95% CI: 0.23 to 0.53) (Table 4.2).[109, 113, 137, 144, 145, 148, 171] Two papers assessed progression of injury on repeat CT imaging and both found initial GCS 15 to be associated with reduced risk of progression.[145, 148] Four studies estimated the effect of an initial GCS of 15 in multivariable models.[109, 137, 144, 171] All 4 multi-variable models found initial GCS15 to be associated with a reduced risk of adverse outcomes.

Severity of Injury as assessed by CT findings

Nine studies estimated whether the severity of injury identified by initial CT scan predicted adverse outcomes.[27, 84, 113, 126, 137, 144, 147, 149, 170] This was assessed by: the presence of midline shift or mass effect in 5 studies,[84, 126, 137, 147, 170] the Marshall classification in 2 studies,[113, 144] and measures of haemorrhage thickness or volume in 4 studies.[27, 126, 149, 170] The variability in the measures of injury severity and differences in the outcomes assessed prevented pooling.

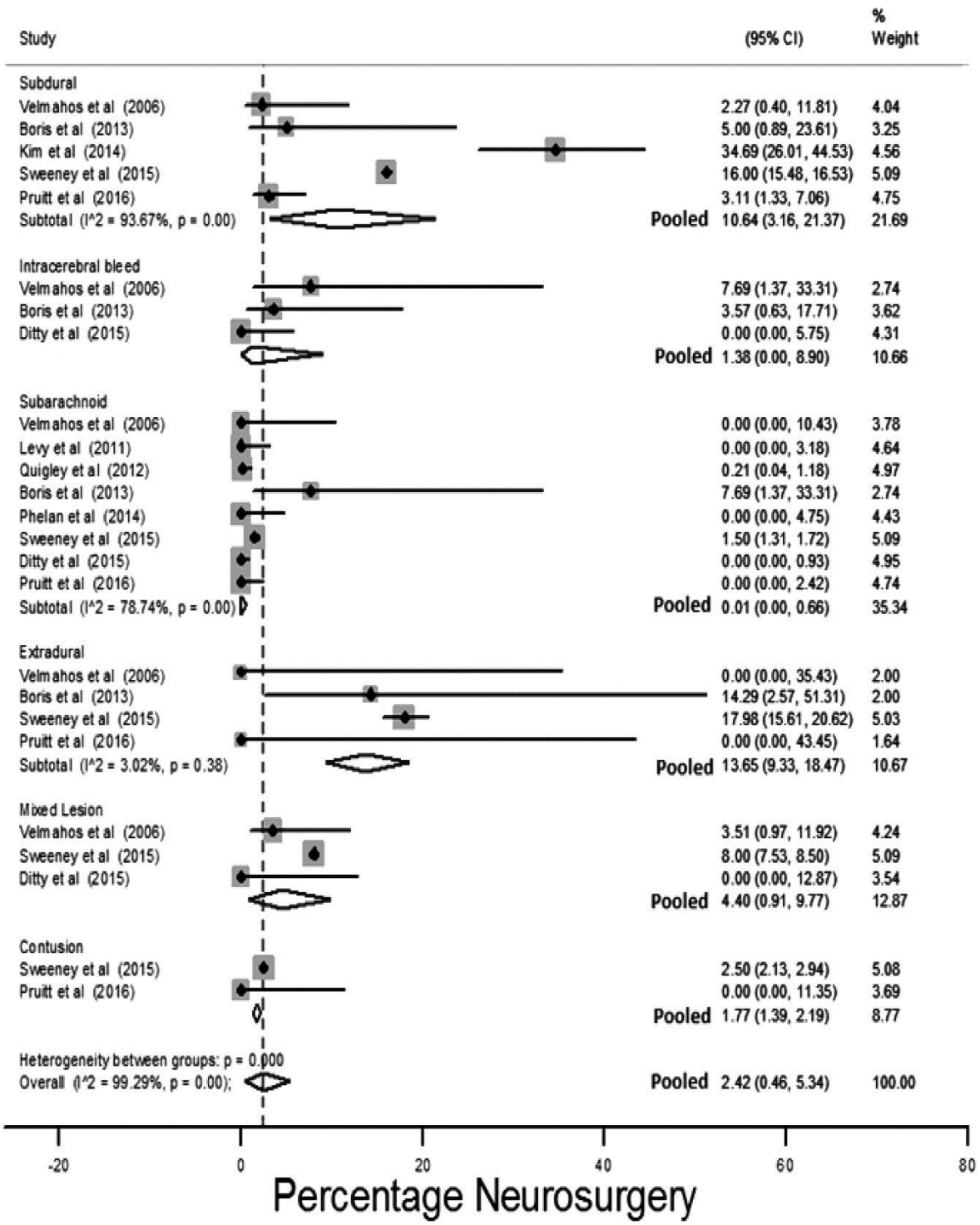
All studies that assessed presence of midline shift/mass effect found it to be statistically predictive of adverse outcomes. This association remained in the 2 studies that presented multivariable analysis.[84, 137] The Marshall classification was assessed as a continuous[144] and dichotomised variable[113] and neither study found a statistically significant association with adverse outcomes.

The 2 studies which assessed the effect of bleed thickness>10mm found this to be statistically predictive of either progression of injury on repeat CT imaging or neurosurgical intervention in both uni and multivariable analysis.[27, 149]

Isolated subarachnoid haemorrhage

Twelve studies presented outcomes for populations with isolated injuries and patients with isolated subarachnoid haemorrhages (iSAH) were the lowest risk for adverse outcomes: neurosurgical intervention pooled risk 0.01% (95% CI: 0 to 0.7%) (Fig. 4.11), and 1.1% (95% CI: 0 to 5.5%) pooled prevalence of clinical deterioration (Appendix 28).[104, 109, 126, 130, 142, 145, 148, 168, 169, 173, 177, 178]

Figure 4.11: Pooled risk of neurosurgery stratified by isolated injury type identified by initial CT imaging



Univariable effect estimates presented in the 2 studies that assessed the effect of the presence of iSAH were pooled with data extracted from 3 additional studies. [109, 144,148, 168,

[178] The pooled estimate indicated iSAH reduced the risk of neurosurgical intervention/clinical deterioration (Table 4.2).

Two multivariable models included iSAH as a prognostic factor. One found iSAH to be associated with a lower risk of clinical deterioration.[109]The other found iSAH to have no effect on risk.[168]

Isolated extradural haemorrhage

Patients with isolated extradural haemorrhage had the highest risk of neurosurgical intervention: 13.7% (95% CI: 9.3% to 18.5%) (Fig. 4.11). 18.5% is estimated from a population of all initial GCS14-15 patients with extradural haemorrhage, whilst the estimates in the other studies are from populations that have been selected for more conservative management.[148, 168, 177, 178]

Three studies assessed isolated extradural haemorrhage as a prognostic factor.[109, 144, 168] A pooled risk estimate for clinical deterioration or neurosurgical intervention using these 3 studies and outcome data extracted from a further 2 studies,[148, 178] found isolated extradural haemorrhage to be associated with these outcomes (OR 2.26 95% CI: 1.9 to 2.68) (Table 4.2). Isolated extradural haemorrhage remained statistically associated with neurosurgical outcomes in the only multi-variable model that included this factor.[168]

Anti-coagulation

Twelve studies estimated the prognostic effect of anti-coagulation.[79, 84, 109, 113, 126, 145, 147-149, 168, 170, 171] Measures of anti-coagulation included: any documented coagulopathy,[84, 113, 126, 148, 168, 170] pre-injury warfarin use,[109, 147, 171] warfarin or antiplatelet therapy as a combined risk factor,[149, 170] and continuous laboratory measures of anti-coagulation.[84, 145, 171]

Univariable effect estimates of dichotomous measures of anti-coagulation were pooled with individual patient data from Fabbri et al for the composite outcome of clinical

deterioration or neurosurgical intervention (Table 4.2), pooled estimate: OR 1.45 95% CI: 1.28 to 1.64.

Two studies presented multivariable models that included anti-coagulation and it was not statistically associated with the outcomes of interest in either model.[149, 168]

Anti-platelet medication

The effect of anti-platelet use was evaluated by: aspirin use,[109, 147, 171] clopidogrel use,[109, 147, 171] and a joint measure of antiplatelet use.[126, 137, 158] No multivariable models included antiplatelet use. Pooled univariable risk estimates of pre-injury aspirin and clopidogrel use are presented in Table 4.2. Meta-analysis indicated a statistical association between clopidogrel with clinical deterioration or neurosurgical intervention but no association between aspirin use and this outcome.

Discussion:

Summary

We have completed a thorough systematic review and meta-analysis to identify risk factors for adverse outcomes in this TBI population. This is the first review to provide pooled estimates of clinically important outcomes in this population and identify which factors affect the risk of these outcomes.

The pooled prevalence of adverse outcomes were: 11.7% (95% CI: 8.21 to 5.8%) clinical deterioration, 3.5% (95% CI: 2.2 to 4.9%) neurosurgical intervention, and 1.4% (95% CI: 0.8% to 2.2%) death. These outcome estimates used a pooled total of 65724 patients and are comparable to the 2.7% craniotomy rate reported for a similar population in a national UK trauma database.[8] The variation in individual study outcomes reflects differences in populations studied and outcome definitions. For the outcomes of neurosurgical intervention and death heterogeneity could be explained by the age of study populations and different study population GCS scores.

Risk factors for adverse outcomes were identified using both meta-regression of study characteristics and synthesis of prognostic models presented by primary studies. Age, anti-coagulation and initial GCS were found by both methods to affect risk. An increase in mean study population age by 1 year was associated with increased odds of neurosurgical intervention of 1.09 in multivariable meta-regression (Table 4.1) and age was a predictor of an adverse outcome in 6/11 multivariable models presented in primary studies. In univariable meta-regression a unit increase in the percentage of the study population taking anti-coagulants was associated with a 1.1 increase in the odds of neurosurgical intervention (Table 4.1). Pooling of univariable models presented in primary studies found anticoagulated patients to have odds 1.45 time greater than patients not anticoagulated for neurosurgical intervention/clinical deterioration (Table 4.2). In multivariable meta-regression, a unit increase in mean/median study population GCS was associated with an 0.12 reduction in the odds of neurosurgical intervention (Table 4.1). Pooling of univariable models indicated that patients with initial GCS<15 had odds of clinical deterioration/ neurosurgical intervention 2.9 times that of patients that presented with an initial GCS of 15 (Table 4.2). In multivariable meta-regression models including both initial GCS and age, initial GCS had a smaller effect on the risk of either neurosurgical intervention or death than in univariable analysis and this may be due to older patients presenting with higher initial GCS relative to the severity of their injury (Table 4.1).[209] Patients with extradural haemorrhage had the highest prevalence of adverse outcomes, whilst patients with isolated subarachnoid haemorrhage had the lowest (Fig. 4.11).

Meta-analysis of multivariable models was not possible due to the small number and variability in how these models were constructed. Therefore, although this review has identified the factors that affect risk, no model that could identify low-risk patients was found or could be reliably constructed.

Strengths

A thorough search has been conducted, identifying 50 relevant primary studies. Our review fulfils all the AMSTAR systematic review checklist quality domains apart from items 10 and 11, regarding the assessment of publication bias and conflicts of interest.[210]

However, the non-interventional nature of the included studies means these domains are less relevant. This review is low-risk for bias in the 5 domains assessed by the Risk of Bias in Systematic reviews (ROBIS) tool.[211]

Limitations

Many studies identified were small and retrospective with limited follow up of patients after discharge. Instead of attempting to identify low-risk patients through prognostic modelling, several studies selected patients on study specific characteristics for different care pathways. This variation in study populations contributed to heterogeneity in estimates of outcome prevalence and risk factor effect. The prognostic models that were identified were often derived in cohorts too small to construct multivariable models with all relevant factors. The clinically useful outcome in informing discharge decisions is clinical deterioration, and most prognostic models did not assess this.

Clinical deterioration was defined by 7 different composite outcomes and most commonly by neurological deterioration. This lack of consistency in definition contributed to the heterogeneity in outcome estimates. Neurological deterioration was variably defined and a clinically relevant and consistently used definition or deterioration is required.

No included studies assessed pupillary response and duration of loss of consciousness/amnesia. These factors are predictive of adverse outcomes in other TBI populations and future research should assess these factors in this population.[88, 212]

Context

When the Canadian CT Head Rule was developed, the authors presented a consensus derived list of intra-cranial injuries that would never require neurosurgical intervention.[9] The implication was that patients with such injuries were safe for discharge. This was rejected by the Society of British Neurological Surgeons.[1] A US group based in Arizona has produced the BIG consensus derived statement that identifies a population with low risk

clinical characteristics and intra-cranial injuries similar to those presented by the CCHR authors.[31] They propose such patients are safe for discharge after 6 hours of ED observation.[31, 80, 81]

Kreitzer et al present an alternative policy at a level 1 trauma centre in Cincinnati where the population of interest remain in the ED for observation and undergo repeat CT imaging approximately 6 hours following diagnosis.[157] Neurologically stable patients without progression of injury are discharged. Pruitt et al present a model of care in a Level 1 trauma centre in Chicago in which all GCS13-15 patients with intra-cranial injuries receive a neurosurgical consultation.[178] Low risk patients identified by the neurosurgeon are left under ED care and discharged after a period of observation. This is similar to the standard of care in the UK NHS.

Others advocate the admission of GCS13-15 patients and brain injuries identified by CT imaging to higher levels of care and routine re-imaging, citing evidence that deterioration in neurological examination may not identify progression of injury that warrants clinical intervention.[84, 149] Multiple reviews have found that this is too rare an occurrence to warrant routine re-imaging of all GCS13-15 patients with TBI identified by CT.[92-95]

Implications

This review supports the view that there are subsets of GCS13-15 patients with injuries identified by CT imaging that may possibly be safely routinely discharged from the ED. However, the current available evidence is insufficient to reliably identify such low-risk patients. The risks of serious adverse outcomes are sufficiently high that, in the absence of evidence to be able to accurately pin point low-risk individual patients, admission for observation probably remains clinically indicated.

No validated model predicting a measure of clinical deterioration that could be used to triage hospital admission was identified. We suggest future research should assess a measure of clinical deterioration that encompasses: neurosurgical intervention, death, a

fall in GCS by 2 or more points, seizure activity, intravenous medical intervention or ICU intervention. These would warrant ongoing inpatient hospital admission.

The BIG criteria, although the best effort at risk stratifying this group in a clinically relevant way, require validation in larger prospective cohorts in different healthcare contexts before being more widely adopted. They were derived by consensus, and empirical prognostic modelling could possibly improve the accuracy of risk stratification.

Decision rules have been employed successfully in the ED to risk stratify patients in a range of conditions, including ankle injuries and suspected pulmonary embolus.[213, 214] Equivalent models could be used for patients with mTBI to identify low-risk patients. This review has identified the key factors that are likely to inform such risk stratification, but an adequately powered derivation study with a clinically relevant definition of deterioration and adequate follow up is required.

Conclusion

Mild TBI patients with injuries identified by CT imaging are a heterogenous group. Their overall risk of clinical deterioration and more serious adverse outcomes is small, but clinically significant. Current research gives an indication to which factors affect the risk of adverse outcomes but is of too low quality to inform clinical decision making. High quality prognostic modelling is needed to help inform discharge decisions.

Chapter 5: A protocol for the development of a prediction model in Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge?

Chapter Introduction

This chapter presents the text of a paper published in the Journal of Diagnostic and Prognostic Research in April 2018.[33] The text is identical to that published except for reference, table and figure numbers and the use of UK English spelling. In addition, text has been amended on pages 122 and 125 regarding the distinction between sensitivity and negative predictive value. Supplementary Material is presented in the thesis appendices and references to these materials have been changed in accordance with this.

Abstract

Background

Head injury is an extremely common clinical presentation to hospital Emergency Departments (ED). Nine-five percent of patients present with an initial Glasgow Coma Scale (GCS) score of 13-15, indicating a normal or near normal conscious level. In this group around 7% of patients have brain injuries identified by CT imaging but only 1% of patients have life-threatening brain injuries. It is unclear which brain injuries are clinically significant, so all patients with brain injuries identified by CT imaging are admitted for monitoring. If risk could be accurately determined in this group admissions for low-risk patients could be avoided and resources could be focused on those with greater need.

This study aims to: (a) estimate the proportion of GCS13-15 patients with traumatic brain injury identified by CT imaging admitted to hospital who clinically deteriorate (b) develop a prognostic model highly sensitive to clinical deterioration which could help inform discharge decision making in the ED.

Methods

A retrospective case note review of 2000 patients with an initial GCS13-15 and traumatic brain injury identified by CT imaging (2007-2017) will be completed in two English major trauma centres. The prevalence of clinically significant deterioration including death, neurosurgery, intubation, seizures or drop in GCS by more than 1 point will be estimated. Candidate prognostic factors have been identified in a previous systematic review. Multivariable logistic regression will be used to derive a prognostic model and its sensitivity and specificity to the outcome of deterioration will be explored.

Discussion

This study will potentially derive a statistical model that predicts clinically relevant deterioration and could be used to develop a clinical risk-tool guiding need for hospital admission in this group.

Key Words:

Mild Traumatic Brain Injury; Prognosis; Predictive model; Intra-cranial haemorrhage; Minor Head Injury

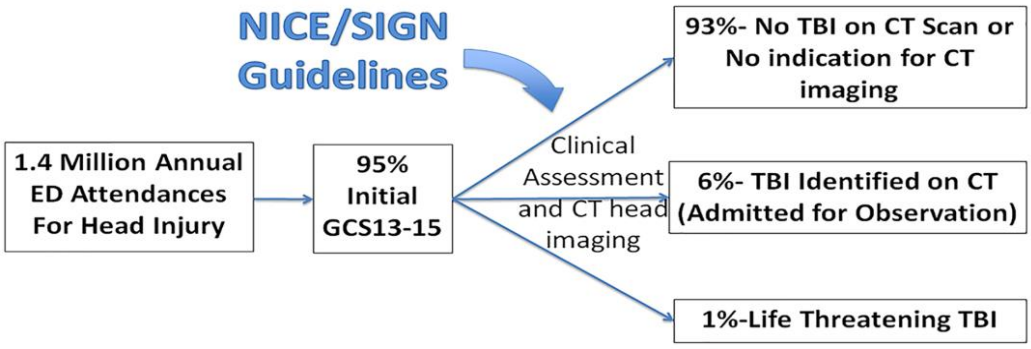
Authors' contributions

I conceived the idea for this study with help from my supervisors Trevor Sheldon, Fiona Lecky and Victoria Allgar and this formed part of my NIHR Doctoral Research Fellowship application. Andrea Fabbri helped refine the proposed outcome measures and provided a data set for potential inclusion in the final study. Trevor Sheldon and Fiona Lecky provided specialist advice prognostic methodology and the design of methods. Victoria Allgar provided specialist statistical advice. Fiona Lecky, Will Townend and Andrea Fabbri provided specialist advice regarding the clinical context. All authors read and approved the final manuscript.

Background

There are 1.4 million annual attendances to Emergency Departments in England and Wales following a head injury.[1] Approximately 95% of patients present with an initial score of 13-15 on the Glasgow Coma Scale (indicating a normal or mildly impaired conscious level) and are defined as having a "minor head injury".[6] Minor head injured patients have a 1% risk of life threatening traumatic brain injury (TBI).[9] In the UK head injury guidelines are used to triage CT imaging in this large patient population with the aim of identifying all life-threatening injuries.[1, 11] Adult guidelines are based on the internationally used and validated Canadian CT Head Rule and are applied to patients aged ≥16.[9, 215] Around 7% of patients have TBI identified by CT imaging.[83] All of these patients are admitted to hospital in the UK due to fears about the risk of deterioration due primarily to intra-cranial haematoma progression, but these risks are not well characterised (fig. 5.1).

Figure 5.1: CT imaging in minor head injury



The management of GCS13-15 patients with CT identified TBI is controversial with some advocating admission to higher levels of care and mandatory repeat CT imaging due to the risk of deterioration.[84] Others argue that some patients are at low enough risk to be discharged safely from the ED after a short period of observation, a model of care adopted in a level 1 trauma centre in Arizona.[31] The UK NICE guidelines (published 2004, 2007 and 2014) state that all patients with significant brain injuries identified by CT imaging should be admitted to hospital, but do not qualify what constitutes such injuries.[1]

In our recent systematic review, we estimated a pooled risk of neurosurgery in GCS13-15 patients with injuries identified by CT imaging of 3.5% (95% C.I. 2.2-4.9%) from the results of 36 studies.[28] A risk of clinical deterioration, such that patients would benefit from inpatient hospital admission, of 11.7% (95% C.I 11.7-15.8%) was derived from 18 studies. There was significant variation in estimates of these outcomes across individual studies and no studies were conducted in the UK where NICE guidelines are used so relevant risk factors were not considered. Following the introduction of the NICE guidelines hospital admissions for head injury increased in England.[18] It is thought this may be due to more injuries of less clinical significant being identified due to increased CT imaging of minor head injured patients.[18] Research is required to estimate the risks of adverse outcomes in GCS13-15 patients with injuries identified by CT imaging in the UK.

GCS13-15 patients with brain injuries identified by CT imaging have a small but clinically important risk of significant adverse outcomes. Well conducted prognostic research could generate models which allow the identification of low-risk patients who could be safely discharged from ED and high-risk patients who would benefit from more aggressive management. Our review identified 41 factors in 21 studies that had been assessed as potentially affecting the risk of adverse outcomes in this group.[28] None of this research was conducted in the UK and no multivariable models were identified that could be used to accurately identify patients at sufficiently low-risk of deterioration to be discharged from the ED. Prognostic research conducted within the context of NHS care is required to assess the extent to which GCD13-15 patients with CT identified TBI can be stratified by risk. This will help refine the NICE guidelines and potentially allow better resource allocation in the management of these patients by identifying those who do not require hospital admission.

Aims:

1) Estimate the prevalence of clinical deterioration in initial GCS13-15 adult patients with brain injuries identified by CT imaging.

2) Develop a multivariable model that accurately identifies adult patients of sufficiently low-risk of clinical deterioration that they could be discharged from the ED.

Methods

Study Design

This a retrospective and consecutive cohort observational study. The proportion of the cohort that clinically deteriorate will be estimated and a multivariable prognostic model that predicts deterioration will be developed. The study will be conducted and reported in accordance with the TRIPOD recommendations.[41, 216]

Patients will be identified through retrospective case note review over a 10-year period from 2007-2017 at Hull Royal Infirmary and Salford Royal Hospital, two English major trauma centres.

Participants

Inclusion criteria: Patients aged ≥16 admitted to hospital, with an initial GCS of 13 or more on presentation to the ED and traumatic brain injury identified definitively by CT head imaging. All patients with epidural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, intra-cerebral haemorrhage, intra-cerebral contusion, skull fractures and any combination of these injuries will be considered for inclusion. All patients with injuries identified by CT that could only be traumatic in aetiology including skull fractures, extradural haemorrhages and subdural haemorrhages will be counted as having traumatic brain injury. Where patients have intracranial haemorrhage identified that could be either traumatic or spontaneous patients will only be included if they have either a documented mechanism or evidence of head injury. This will apply to intra-cerebral and subarachnoid haemorrhages. Included mechanisms are falls, assault, road traffic collision, sport and any other mechanism that could result in blunt trauma above the clavicles. Evidence of head

trauma includes bruising, wounds or injuries above the clavicles including facial and skull fractures identified radiologically.

Exclusion criteria: Patients with obvious penetrating head injury or with spontaneous intra-cranial haemorrhage. Patients will be categorised as having a spontaneous intra-cranial haemorrhage if the haemorrhage could occur spontaneously or traumatically and they have no documented preceding mechanism or evidence of head injury or if the CT report states that the pattern of intra-cranial haemorrhage indicates a spontaneous event. Patients with pre-existing brain injuries or other pathology that makes the interpretation of timing of injury difficult and this includes patients with haemorrhagic brain tumours, chronic subdural haemorrhage or hygromas and other types of pre-existing intra-cranial bleeds. Patients with isolated occipital condyle fractures are excluded as these are treated as cervical spine injuries. Patients transferred from other EDs following identification of a brain injury will also be excluded.

Study outcome

The outcome of interest is a composite measure of clinical deterioration such that inpatient hospital admission was warranted, this includes: death due to TBI or neurosurgery within 30 days of attendance, ICU intervention whilst an inpatient, seizure activity whilst inpatient, drop in GCS by 2 or more points whilst an inpatient, or a readmission to hospital within 30 days of injury related to TBI.

Candidate prognostic factors

Potential candidate factors have been selected a priori by: identification of factors that individually predict deterioration in the study population in our systematic review, inclusion of additional factors that predict adverse outcomes in prognostic models for patients with more severe TBI and trauma and inclusion of factors that represent NICE guideline standards and criteria for treatment and investigation of head injury and TBI.[1,]

[87, 88, 217] All factors being considered for inclusion in the final model are presented in Table 5.1 with the reason for their inclusion.

Comorbidities will be measured using a trauma modified Charlson Comorbidity Index. Brain injury severity, as shown on CT scan, will be stratified using the Marshal Classification, which will be calculated from Abbreviated Injury Severity (AIS) codes for TBI using the method described by Lesko et al.[67, 218] The Charlson Comorbidity Index, AIS and Marshal Classification are internationally validated prognostic scoring systems.[219, 220] Frailty will be assessed using the clinical frailty scale described by Rockwood et al.[221]

Table 5.1: Prognostic factors being investigated

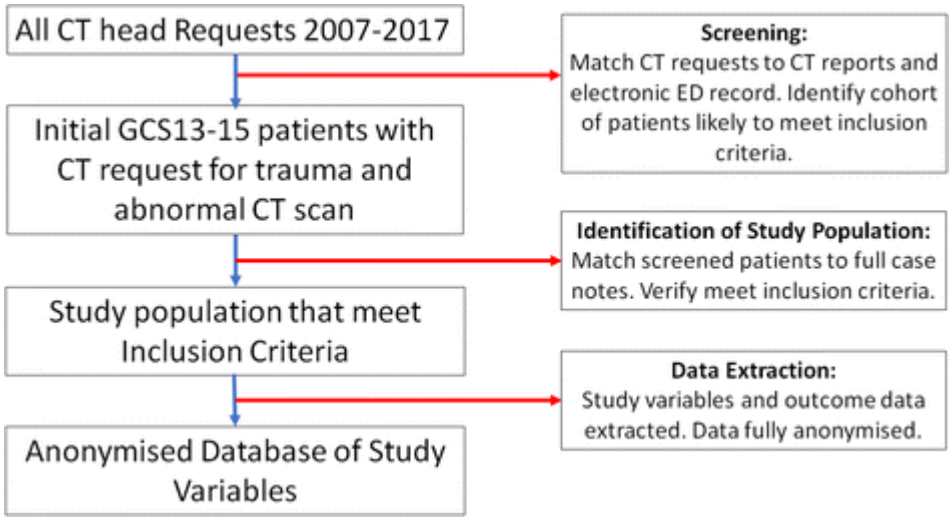
Factors from Systematic Review	Type of Data	Factors from NICE guidelines	Type of Data	Factors from TARN TBI/trauma model	Type of Data
Age	Continuous	1st neurological examination in ED	Categorical	Admission Hb	Continuous
Sex	Categorical	Equal Pupils 1st examination	Categorical	Admission Platelets	Continuous
Pre-injury anti-coagulant use	Categorical	Both Pupils reactive 1st examination	Categorical	Charlson Trauma Modified Comorbidity index	Continuous
Pre-injury anti-platelet use	Categorical	SIGN of Skull fracture 1st examination	Categorical	Admission BM	Continuous
GCS on arrival to ED	Categorical	Seizures in ED	Categorical	Frailty Score	Continuous
BP on arrival ED	Continuous	Vomiting in ED	Categorical		
HAIS	Continuous	An occupant ejected from a motor vehicle	Categorical		
Marshall Classification	Categorical	Mechanism of Injury	Categorical		
Single Injury	Categorical	Amnesia	Categorical		
Comment on Midline shift	Categorical	Intoxicated EToH time of injury	Categorical		
Comment on size of bleed		Seizures before arrival ED	Categorical		
Additional Injuries	Categorical	Vomiting before arrival ED	Categorical		
Sats on arrival ED	Continuous	A pedestrian or cyclist struck by a motor vehicle	Categorical		
		A fall from height of > than 1 metre or 5 stairs	Categorical		

Data collection

Screening

A database of all emergency department CT brain requests and reports for patients aged 16 and over between 2007-2017 will be generated at the 2 sites from the electronic requesting and reporting system. This will be screened to identify potentially eligible patients with CT requests related to head injury and CT scans with reported abnormalities related to TBI or intra-cranial haematomas (Fig. 5.2). Patients identified in this way will be matched to electronic ED case notes, reports and discharge summaries to identify the subset of patients potentially admitted with an initial GCS13-15.

Figure 5.2: Data extraction



Data Extraction

The full case records of patients identified through screening as potentially meeting the inclusion criteria will be retrieved (Fig. 5.2). In patients who are confirmed to meet the inclusion criteria all a priori candidate prognostic factors will be extracted from the case records. Demographic information will be extracted from data recorded at the time of presentation to the ED following head injury. Comorbidities, frailty and pre-injury medication use will be extracted from that recorded in the ED attendance and subsequent inpatient hospital admission documentation. Co-morbidities recorded in the inpatient notes up to 1 year prior to the presentation following head trauma will be included in accordance with the method of data collection in a recent update of the Charlson comorbidity index.[220]

The full inpatient records will be interrogated for evidence of intervention or clinical deterioration that would meet the composite outcome measure. Recorded patient ED and hospital admissions after discharge following the relevant admission for traumatic brain injury will be assessed for evidence of deterioration, intervention or readmission in the 30 days following the initial ED attendance.

Patients who were included in the national Trauma Audit and Research network (TARN) registry will be identified locally. Using an anonymous TARN study number we will assess for any deaths recorded on the TARN registry within 30 days of admission.

Research Team Undertaking Screening and Data Extraction

Members of the direct Emergency Department care team at each NHS trust will undertake the screening of electronic records for patients admitted following head injury and data extraction from case notes. Staff undertaking data extraction will undergo data extraction training and this includes training in abbreviated injury scale coding of injuries on CT brain scans by the Trauma Audit and Research Network (TARN) which is an Association for the Advancement of Automotive Medicine accredited trainer to ensure the use of AIS dictionary in a reliable and reproducible fashion. Data extraction will be

piloted over a 1-month period. Hypothetical and non-identifiable training samples of potential patient records will be generated at both sites during the training period and will be used to check the quality of, and validate, data-extraction in the research team. The research team will not be blinded to outcomes. However, most prognostic variables being collected are demographic and other factors not subject to interpretation. Patients are also not being allocated to treatment groups and therefore data collection is less likely to be biased in favour of a specific outcome.

Sample Size

Sample size of a prognostic study is informed by 3 factors: anticipated prevalence of the outcome (in this study clinical deterioration), desired sensitivity of the model to the outcome and the precision of the 95% confidence interval around the sensitivity of the model.[41]

We have based our sample size on a 10% estimated prevalence of clinical deterioration in our systematic review and our desired precision of the sensitivity of the derived model for this outcome.[28] Research into discharge decision making in patients presenting to the ED with chest pain, indicated that a 1/100 risk of a patient being discharged who subsequently had a significant cardiac event, may be an acceptable risk threshold to both patients and clinicians.[222] Therefore, we will evaluate the negative predictive value for clinical deterioration at a 1% risk threshold as this may correspond to a clinically acceptable level of risk of deterioration in a discharged patient.

A sample size of approximately 2000 patients is required, based upon a desired 99% sensitivity in order that the maximum marginal error of the estimate does not exceed 1.4% with a 95% confidence interval.[223] Based upon previous data collection we estimate at least 100 patients will be eligible for inclusion per year at each site of data collection over the 10 year period of interest.[224]

Statistical analysis

Outcome Estimate

The proportion of patients that fulfil the composite measure of deterioration will be estimated. A sample size of 2000 patients will allow us to estimate the prevalence of clinically significant deterioration with a 1.3% margin of error at a 95% confidence level.

Model Development

Multivariable logistic regression with backward stepwise selection will be used to find the best combinations of candidate factors highly sensitive for detecting deterioration while achieving the maximum possible specificity. This approach is favoured as all correlations between predictors are considered in the modelling procedure and there is easier transparency of reporting.[41]

Candidate prognostic factors with a P value greater than 0.05 will be selected for removal. Forced variables (predictors) that we consider as having clinical relevance, as indicated in our systematic review and the NICE guidelines, will initially also be considered for inclusion in our model and retained in the initial steps of backwards elimination. In the final model all factors that do meet the significance level will be removed.
The sample size of 2000, with an anticipated prevalence of clinical deterioration of around 10%, will allow the model to include 20 variables, based on the rule of at least 10 outcome events per parameter estimated.

Continuous factors will not be categorised initially to avoid a loss of power.[225, 226] Calibration (the agreement between outcome predictions from the model and the observed outcomes) will be tested with the Hosmer–Lemeshow test. We will assess the apparent performance of the fitted models for discrimination using the C-statistic (equal to the area under the receiver-operating characteristic curve) and the sensitivity for clinically significant deterioration.[227]

Internal validation using the bootstrap validation approach will be undertaken to evaluate the performance and optimism of the developed model.[228] This will allow the use of the complete data set for model development and provide a mechanism to account for model overfitting or uncertainty in the model development process. We will quantify any optimism in the final prediction model and estimate a so-called "shrinkage factor" that can be used to adjust the regression coefficients and apparent performance for optimism. This will lead to a new final model being produced in each of the bootstrap samples. We will average the difference in the performance of the models to obtain a single estimate of optimism for the C-statistic.

Missing Data

As data are to be extracted from clinical records, missing variable data will inevitably occur. Although it is possible to verify the data to judge whether missing data are missing completely at random (MAR) or associated with observed variables, it is generally impossible to prove that data are indeed MAR or whether they are not missing at random. (MNAR).[225] Multiple imputation will be used to impute with the number of imputations determined by the amount of missing data, under a missing at random assumption, so as to avoid excluding patients from the analysis. This will be completed using STATA with the exact method determined by the amount, type and distribution of the missing data and we will adhere to recognised guidelines for appropriate use and reporting of methods to deal with missing data.[229, 230] After imputation, a sensitivity analysis will be undertaken to determine how the substantive results depend on the multiple imputation method employed. This is consistent with the TRIPOD recommendations with the handling of missing data in prognostic studies.[41]

Model Accuracy

The sensitivity and specificity of the model for detecting patients at low-risk of deterioration will be calculated comparing the classification of each patient by the model

with whether they actually deteriorated. To assess how informative lack of deterioration is, the model will be derived again for those patients who do not deteriorate within 24 hours. We will determine whether a more accurate model can be produced for those still in hospital after 24 hours.

A Receiver Operating Characteristic (ROC) curve for both models will be plotted and the trade-off between the sensitivity and specificity of the model explored.[231] As indicated previously a 1/100 risk of deterioration following discharge may be clinically acceptable and therefore when applying our model to select patients for discharge we will aim for a very high sensitivity to deterioration which will correspond to a negative predictive value of around 99%.[222]

Sensitivity analysis

The 10-year period of data collection represents a long-time period over which clinical practice and outcomes may have changed. To assess for this, we will estimate the yearly prevalence of clinical deterioration and note any statistically significant changes in outcome over time. In addition, because NICE guidelines were updated in 2014 (with minor changes to the indications for CT brain imaging) the prognostic model will be estimated solely for the time-period 2014-2017 and compared to the model estimated for the whole-time period.[1]

Exploratory Analysis

Individual patient data from a prospective Italian cohort study is available to the research team.[79] The variables collected in the Italian study and how they compare to the variables being collected in our study are shown in Table 5.2. If most factors present in the multivariable model developed in our study are present in the Italian data set then we will assess the effect of these factors on the risk of deterioration in a multivariable model derived in the Italian data set. If the effect estimates are similar to those estimated in the

data collected in England then we will combine the individual patient data of the 2 data sets to improve the precision of the model estimates.

Table 5.2: Comparison between Italian data set and data being collected

Factor	**In Italian Data**	**Factor**	**In Italian Data**
Age	Yes	Equal Pupils 1st examination	Yes
Sex	Yes	Both Pupils reactive 1st examination	Yes
Pre-injury anti-coagulant use	Yes	SIGN of Skull fracture 1st examination	No
Pre-injury anti-platelet use	No	Seizures in ED	No
Charlson Trauma Modified Comorbidity index	Yes	Vomiting in ED	No
A pedestrian or cyclist struck by a motor vehicle	Yes	HAIS	No
An occupant ejected from a motor vehicle	Yes	Marshall Classification	Yes
A fall from height of > than 1 metre or 5 stairs	Yes	Single Injury and type of injury	Yes
Mechanism of Injury	No	Comment on Midline shift	No
Amnesia	Yes	Comment on size of bleed	No
Loss of Consciousness	Yes	Frailty Score	No
Intoxicated time of injury	No	Admission Hb	No
Seizures before arrival ED	Yes	Admission Platelets	No
Vomiting before arrival ED	Yes	Admission BM	No
GCS on arrival to ED	Yes	Additional Injuries	Yes
BP on arrival ED	No		

Discussion

Strengths

To the authors' knowledge this will be the largest cohort study conducted that assesses clinical deterioration in GCS13-15 patients with brain injuries identified by CT imaging. We are collecting data from multiple sites and potentially incorporating data from a different European country. The definition of clinical deterioration is wide and defined to encompass potential benefits of hospital admission from the ED. This outcome is one that can be used to help inform clinical decision making regarding the selection of patients in this group that would benefit from hospital admission.

Limitations

Data collection is retrospective and will be limited by the nature and accuracy of the data clinically recorded. However, such data are likely to be applicable and implementable in current routine practice. Given the large sample size required for this study and the challenges of prospectively recruiting patients in the ED, a retrospective method for data collection represents a feasible and pragmatic data collection strategy.

Outcomes will only be assessed during hospital admission and for those who re-attend the study hospitals following discharge. This may underestimate deterioration following discharge especially if patients die in the community or deteriorate and are readmitted to a different hospital. We will estimate the effect of this possible bias by conducting a sensitivity analysis using data for the sub-set of patients registered on the Trauma and Audit Network Database where complete data following discharge is available.

Further Research

Prognostic models tend to perform optimistically using the data from which they were derived and therefore their accuracy requires external validation in separate data sets.[41]

There are different strategies for this and we will attempt to validate the model derived from this study in a sub-population of a European prospective cohort of TBI patients that is currently ongoing (CENTER-TBI), with data expected to be available in 2018.[232, 233] Our validation study will be subject to a separate protocol. If the model appears sufficiently accurate at identifying low-risk TBI patients could be safely discharged implementation will be tested prospectively in the context of the NHS.

Abbreviations:

AIS: Abbreviated Injury Severity Score; CT: Computed Tomography; GCS: Glasgow Coma Scale; NICE: National Institute for Health and Clinical Excellence; ROC: Receiver Operating Curve; TBI: Traumatic Brain Injury; TARN: The Trauma Audit and Research Network

Declarations

Ethics Approval and consent to participate

This study received ethical approval from the West of Scotland NHS Research Ethics Committee 4, reference 17/WS/0204.

Patient and Public Involvement

The Hull and East Yorkshire NHS hospital trust have a patient public involvement group, The Trans-Humber-Research Panel, that includes current and previous patients and carers. This group has helped formulate the research aims and protocol for this project. They will have an ongoing role in the project.

The Headway Charity have been consulted in formulating the project aims and will be involved in dissemination of the project findings.

Chapter 6: Development of a clinical decision rule for the early safe discharge of patients with mild traumatic brain injury and findings on CT brain scan: a retrospective cohort study.

Chapter Introduction

This chapter presents the text of a paper submitted to the Journal of Neurotrauma in June 2019. The text is identical to that submitted except for reference, table and figure numbers. Supplementary Material is presented in the thesis appendices and references to these materials have been changed in accordance with this.

Abstract

International guidelines recommend routine hospital admission for all patients with mild traumatic brain injury (TBI) who have injuries on CT brain scan. Only a small proportion of these patients require neurosurgical or critical care intervention. We aimed to develop an accurate clinical decision rule to identify low risk patients safe for discharge from the emergency department (ED) and facilitate earlier referral of those requiring intervention.

A retrospective cohort study of case-notes of patients admitted with initial GCS13-15 and injuries identified by CT was completed. Data on a primary outcome measure of clinically important deterioration (indicating need for hospital admission) and secondary outcome of neurosurgery, ICU admission or intubation (indicating need for neurosurgical admission) were collected. Multivariable logistic regression was used to derive models and a risk score predicting deterioration using routinely reported candidate variables identified in a systematic review. We compared the performance of this new risk score with the Brain Injury Guideline (BIG) criteria, derived in the USA.

1699 patients were included from 3 English Major Trauma Centres. 27.7% (95% CI: 25.5% to 29.9%) met the primary, and 13.1% (95% CI: 11.6% to 14.8%) met the secondary, outcome of deterioration. The derived clinical decision rule suggests that patients with

simple skull fractures or intracranial bleeding less than 5mm in diameter who are fully conscious could be safely discharged from the Emergency Department. The decision rule achieved a sensitivity of 99.5% (95% CI: 98.1% to 99.9%) and specificity of 7.4% (95% CI: 6% to 9.1%) to the primary outcome. The BIG criteria achieved the same sensitivity but lower specificity (5%).

Our empirical models showed good predictive performance and outperformed the BIG criteria. This would potentially allow ED discharge of one in twenty patients currently admitted for observation. However prospective external validation and economic evaluation is required.

Key Words:

Mild Traumatic Brain Injury; Prognostic modelling; Intra-cranial haemorrhage; Minor Head Injury.

Authors' contributions

I conceived the idea for this study with help from my supervisors Trevor Sheldon, Fiona Lecky and Victoria Allgar and this formed part of my NIHR Doctoral Research Fellowship application. Hadir Elbeltagi, Faye Johnson and Eimhear Quinn completed data collection at Salford Royal Hospital. Silvia Tarantino completed data collection at Addenbrooke's Hospital. I completed data collection at Hull Royal Infirmary. I completed the analysis with specialist advice regarding research methods and prognostic modelling from Trevor Sheldon, Victoria Allgar and Fiona Lecky. Fiona Lecky, Angelos Kolias, Peter Hutchinson and Will Townend provided specialist advice regarding the clinical context and application of the research. All authors read and approved the final manuscript.

Background

Over 1.4 million patients annually attend Emergency Departments (EDs) in the UK following head trauma of which ninety-five percent have a normal or mildly impaired conscious level at presentation - Glasgow Coma Scale (GCS) score of 13-15.[1] The majority of Emergency Department Computed Tomography (CT) scans for diagnosing Traumatic Brain Injury (TBI) are conducted in these patients with apparently mild injury. In this group the prevalence of brain injuries, skull fractures and intracranial bleeding is 7%, whilst only 1% of CT scans identify life-threatening TBI.[83]

The management of patients with mild TBI and injuries identified by CT imaging is controversial. Some centres advocate that all patients should be admitted under specialist neurosurgical care and undergo repeat CT imaging.[28, 29] The Brain Injury Guideline criteria (BIG), a consensus derived risk tool currently used in some centres in the USA, advocate the discharge of selected GCS 13-15 patients from the ED with injuries on CT (Appendix 29).[31] We recently published a systematic review of predictors of deterioration in this cohort identifying some single factors associated with deterioration, but there was no good empirical evidence to guide post imaging management in this group[4.]

In England national (National Institute of Health and Clinical Excellence - NICE) head injury guidelines recommend that patients with TBI identified by CT are admitted to hospital.[1] However, they do not define which injuries are clinically significant and which patients benefit from specialist neurosurgical care. Other guidelines used internationally also recommend routine hospital admission for this group.[28]

There has been a paucity of research to inform the admission and referral decisions for these TBI patients with apparently mild injuries but abnormalities on CT scan.[33] Prediction modelling may help identify low risk patients who could be safely discharged from the ED. Modelling may also facilitate earlier identification of patients requiring neurosurgical intervention.

The study aims were to:

I) Estimate the prevalence of clinically important deterioration in GCS13–15 patients with traumatic CT abnormalities.

II) Develop prediction models for patient deterioration that could be used to triage hospital admission and specialist referral.

III) Compare the performance of an empirically derived prediction model with the BIG criteria.

Methods

Study Design

We conducted a retrospective cohort study using case note review of TBI patients presenting to the ED between 2010-2017 at three Major Trauma Centres in England: Hull University Teaching Hospital NHS Trust, Salford Royal NHS Foundation Trust and Addenbrooke's Hospital (Cambridge University Hospitals NHS Foundation Trust). A detailed study protocol has previously been published.[33] The study was conducted and is reported in accordance with international guidelines for prognostic research.[41]

Study Population

Population selection

Within each study centre ED, CT brain scan requests and reports were screened to identify patients with traumatic findings presenting between 2010-17. Patients were matched to case records and if meeting the inclusion criteria data were extracted on patient deterioration outcomes and candidate predictors (see below).

Inclusion Criteria

Patients aged ≥16 with a presenting GCS 13-15 who attended the ED following acute head trauma and had injuries reported on CT brain scan. The latter was defined as: skull fractures, extradural haemorrhage, subdural haemorrhage with an acute component, intra-cerebral haemorrhage, contusions, subarachnoid haemorrhage and intra-ventricular haemorrhage. Intra-cerebral, intra-ventricular and subarachnoid haemorrhages were considered traumatic in aetiology when a mechanism of injury or injuries indicating trauma were recorded.

Exclusion Criteria

Patients were excluded where: a non-traumatic cause of intra-cranial haemorrhage was indicated, pre-existing CT abnormality prevented determining whether acute injury had occurred and patients transferred from other hospitals.

Outcomes

Primary Outcome

A composite measure of deterioration up to 30 days following ED attendance was used including: death attributable to TBI, neurosurgery, seizure, a drop in GCS>1, ICU admission for TBI, intubation or hospital readmission for TBI. Where reason for death, ICU admission or readmission was unknown it was attributed to TBI deterioration.

Secondary Outcome

A composite measure indicating need for neurosurgical specialist admission was used including: neurosurgery, ICU admission for TBI or intubation up to 30 days following ED attendance.

Predictors

Pre-injury anticoagulant and antiplatelet therapy were combined in a variable with two categories: i) no therapy and ii) use of either or both medications (exploratory multivariable modelling indicated they had similar effect sizes). Comorbidity was measured using the trauma modified Charlson comorbidity index. [67] Rockwood frailty scale scores were assigned to patients over 50 years using information in the case notes and data collapsed into established categories.[221, 234]

Appendix 30 outlines how injuries described in written CT reports were categorised. Injuries were coded using the abbreviated injury scale (AIS), injury size and presence of midline shift or mass effect. AIS codes were mapped to the Marshall classification using the method described by Lesko et al and the description of midline shift.[218] An additional category of severity of up to 2 injuries with a combined maximal diameter less than 5 mm was added.

Sample Size

A sample size requirement of 2000 patients was calculated using an estimated prevalence of deterioration of 10%.[33] Interim analysis found the actual prevalence of deterioration to be around 25%. Therefore the target was revised to 1700 patients, equating to 425 events and allowing 42 candidate factors to be assessed on the basis of 10 events per factor.[235]

Statistical analysis

Model Selection

The primary and secondary outcomes of deterioration were modelled as binary variables using logistic regression.[236] We used stepwise selection to find the smallest number of candidate explanatory variables that accurately predict deterioration. Table 6.2 summarises how candidate variables were included in modelling. For each candidate predictor an unadjusted odds ratio was calculated.

The extent of missing data on each candidate variable is shown in Table 6.1. Where medication use was undocumented it was taken to indicate no pre-injury use. For other variables we assumed missing data occurred at random. 25 imputed data sets were created (based on missing data in around 25% of cases) using chained equations including all candidate variables and outcomes in the ICE STATA package.[237] The midiagplots STATA function was used to compare the distributions of observed and imputed data.[238] Where continuous variables were non-normally distributed and implausible imputed values were generated, predictive mean matching was used.[237]

Model selection was performed using multivariable backward elimination with a statistical significance threshold of 0.1. All candidate predictors were initially included and imputed data sets combined using Rubin's rules at each stage of model selection. For candidate continuous variables, rather than assume a linear relationships, the best predictive form was explored with the MFPMI function using backward elimination for fractional polynomial functions in multivariable modelling.[239] [240] Fractional polynomials were limited to 2 degrees of freedom when predicting the secondary outcome.

Model performance

Model fit was assessed using the Briers score averaged across imputed data sets.[241] A score of 0 implies perfect prediction and 0.25 no predictive value.

Model discrimination (how well patients with and without deterioration were distinguished) was assessed by the C-statistic, measured by combing estimates across imputed data sets using Rubin's rules.[240, 242]

Calibration measures how well predictions made by models match observations.[236] The calibration slope of selected predictors was calculated in each imputed data set and averaged.

Sensitivity analysis

Model selection and evaluation of model performance was repeated in patients with complete data.

Internal validation

Models tend to perform better on data from which they are derived (overfitting).[236] Bootstrap internal validation with 100 bootstrap samples was performed in each imputed data set to calculate the average optimism. Model selection was repeated in each bootstrap sample and performance of models selected was subtracted by performance in the original data set.[243, 244] The pooled average difference in the calibration slope between the bootstrap samples and original data was averaged across imputed data sets. This was subtracted from the original averaged calibration slope to estimate the shrinkage factor. The shrinkage factor was applied to the derived model coefficients to adjust for optimism.[236] The C statistic was adjusted for optimism using the same method.

Mild TBI Risk score development and comparison to the BIG criteria

To use our prognostic model for making to clinical decisions we derived a risk score using optimism adjusted coefficients.[245] To make the risk score clinically interpretable coefficients were standardised and rounded.[245] Individual patient risk scores were calculated. A risk score for ED discharge was proposed based on the trade-off between risk of deterioration in a discharged patient and number of patients admitted for observation.

Sensitivity and specificity of the proposed discharge score and of the BIG criteria to deterioration were calculated and compared in patients with complete data for both criteria.

Ethics

NHS Research Ethics Committee Approval was granted by West of Scotland REC 4 reference: 17/WS/0204. As a retrospective case review conducted by members of the direct care team, consent was not requited.

Results

Study population

Figure 6.1 summarises study population selection and Table 6.1 population characteristics and candidate variables. The cohort was mostly male, with around half of patients aged over 60 and quarter with either pre-injury anti-coagulant or anti-platelet use. 470 patients (27.7%; 95% CI: 25.5% to 29.9%) clinically deteriorated as defined by the primary outcome. 223 patients (13.1%; 95% CI: 11.6% to 14.8%) underwent neurosurgery, were admitted to ICU or were intubated (secondary outcome). 72 patients had deaths attributable to TBI. 471 patients had data missing from at least one candidate variable.

Figure 6.1: Population Selection

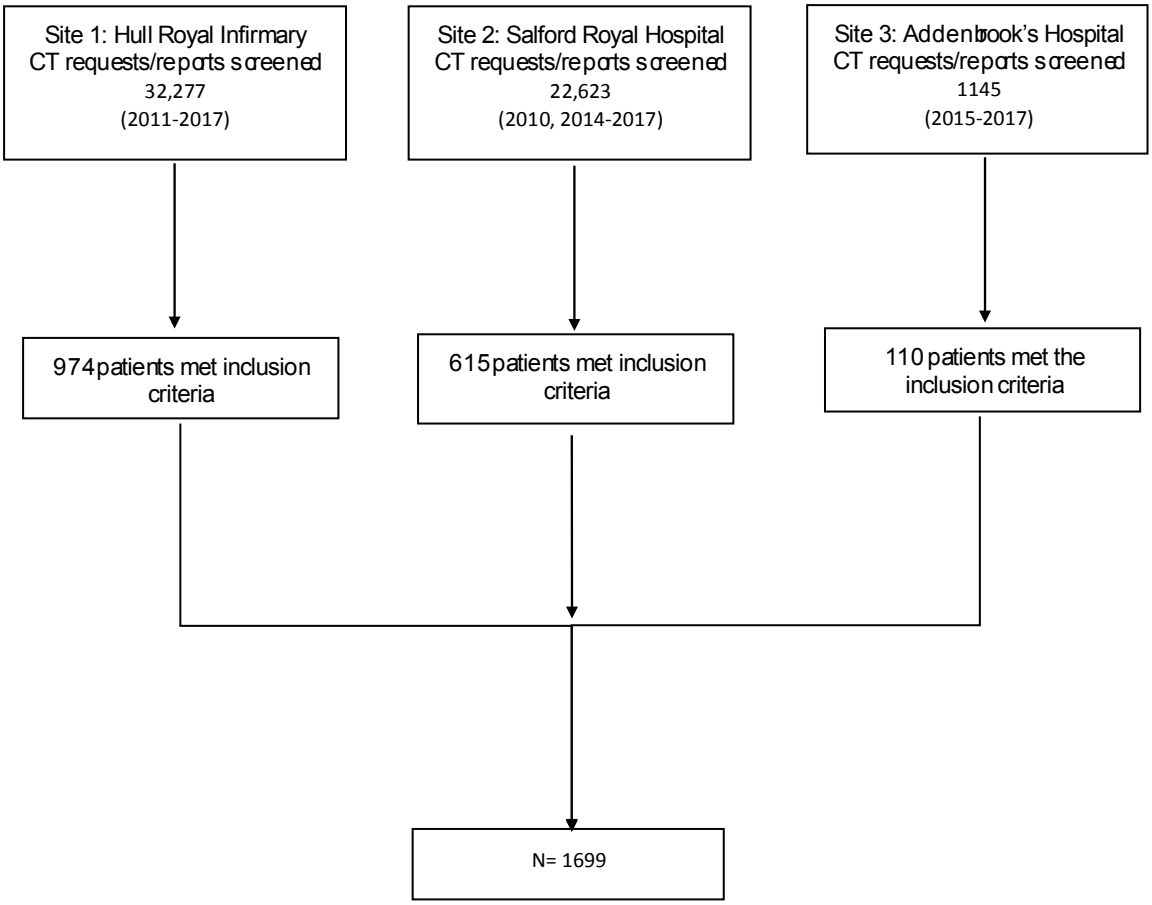


Table 6.1: Characteristics of the study population

Candidate Factor	Category	Mean (SD), min-max or N (%)	Missing data N=1699
Age	Years	58.2 (SD 23.3) 16-101 Age≥65 = 44.9%	None
Sex	Male Female	67% (Median Age= 52) 33% (Median Age= 69)	None
GCS	15 14 13	976 (58%) 533 (31%) 185 (11%)	5 (0.3%)
Mechanism of Injury	Assault Fall Fall from height RTC Sport Other	228 (13%) 1090 (64%) 361 (21%) 298 (18%) 21 (1%) 30 (2%)	31 (1.8%)
Intoxicated	Yes	494 (29%)	38 (2.2%)
Seizure pre-hospital or in ED	Yes	74 (4%)	10 (0.6%)
Vomit pre-hospital or in ED	Yes	310 (18%)	12 (0.7%)
Preinjury Anti-coagulation or anti-platelets	Anticoagulation use Antiplatelet use Both	155 (9%) 294 (17.3%) 8 (0.5%)	None
Abnormal First Neurological Examination	Yes	233 (14.5%)	89 (5.2%)
Initial Blood pressure	Mean Arterial Pressure mmHG	98.5 (SD 17) 43-193	61 (3.6%)
Initial Oxygen Saturation	%	97.4 (SD 2.4) 80-100	59 (3.5%)
Initial Respiratory Rate	RR per Min	17.9 (SD 3.5) 10-48	94 (5.5%)
Haemoglobin	Grams/litre	136 (SD 19.1) 68-265	211 (12.4%)
Platelet Value	10^9/L	232 (SD 77) 2-742	211 (12.4%)
Number of Injuries on CT	1 2 3 4 5 Multiple diffuse injury*	824 (48.5%) 400 (23.6%) 217 (12.7%) 142 (8.4%) 103 (6.1%) 13 (0.8%)	None
Injury severity on CT	**1)** Simple Skull Fractures	66 (3.9%)	None

(Modified Marshall Classification described in detail supplementary Material)	**2)** Complex Skull fractures **3)**1-2 bleeds < 5mm (total) **4)** No or minimal mass effect **5)** Significant midline shift **6)** High/mixed-density lesion **7)** Cerebellar/Brain stem injury	123 (7.2%) 208 (12.2%) 1001 (58.9%) 159 (9.4%) 122 (7.2%) 22 (1.2%)	
Skull Fracture (simple)	Yes	316 (19%)	None
Skull Fracture (complex)	Yes	360 (21%)	None
Contusion	Yes	580 (34%)	None
Extradural bleed	Yes	135 (8%)	None
Intraparenchymal haemorrhage	Yes	240 (14%)	None
Subdural bleed	Yes	694 (41%)	None
Intra-ventricular bleed	Yes	50 (3%)	None
Subarachnoid bleed	Yes	536 (32%)	None
Rockwood Clinical Frailty Scale (CFS)	Patients under 50 CFS 1-3 CFS 4-6 CFS 6-9	649 (39%) 642 (38%) 308 (18.5%) 72 (4.5%)	28 (1.6%) cases
Comorbidity	Charlson Index	1.4 (SD 2.9) 0-28 (range)	20 (1.2%) cases
ISS	Body regions excluding head	5.2 (SD 5.2) 0-75 (range)	None

*diffuse injuries refer to multiple tiny intracerebral haemorrhages/contusions/diffuse axonal injuries

Model selection

Table 6.2 summarises the univariable associations between candidate variables and the primary outcome. Appendix 31 presents the distributions of imputed data.

The equivalent of 41 candidate factors were assessed in multivariable modelling to predict patient deterioration and 34 factors were assessed in modelling to predict need for neurosurgical referral. The selected model predicting the primary outcome is presented in Table 6.2 and the secondary outcome in Table 6.3. Appendix 32 presents a complete case sensitivity analysis.

Table 6.2: Candidate factor (uni and multi-variable) associations with the outcome of deterioration

Candidate Factor	Category	Univariable effect on risk of deterioration : Odds ratio (95% CI)	Multivariable effect on risk of deterioration: Odds Ratio (95% CI)
GCS Vs 15	GCS14 GCS13	1.8 (1.4 to 2.3) 3.1 (2.3 to 4.4)	1.6 (1.2 to 2.1) 2.3 (1.6 to 3.3)
Preinjury Anti-coagulation or anti-platelets	Yes	1.7 (1.3 to 2.1)	1.4 (1.03 to 1.8)
Abnormal Neurological Examination	Abnormal	2.3 (1.7 to 3)	1.7 (1.2 to 2.3)
Haemoglobin	Grams/litre (1 unit increase)	0.99 (0.98 to 0.99)	0.99 (0.98 to 1)
Number of Injuries on CT Vs 1	2 3 4 5 Diffuse injury	1.4 (1.1 to 1.9) 1.8 (1.3 to 2.5) 3.2 (2.2 to 4.7) 3.7 (2.5 to 5.7) 1.1 (0.3 to 4.2)	1.3 (0.97 to 1.8) 1.6 (1.1 to 2.3) 2.5 (1.6 to 3.8) 2.8 (1.7 to 4.6) 1.4 (0.3 to 5.3)
Injury severity on CT Vs simple skull fracture (categories described in detail supplementary material 2)	2) Complex Skull fractures 3)1-2 bleeds < 5mm (total) 4) No or minimal mass effect 5) Significant midline shift 6) High/mixed-density lesion 7) Cerebellar/Brain stem injury	1.4 (0.5 to 4.2) 1.4 (0.5 to 3.8) 4 (1.6 to 10) 13.7 (5.2 to 35.8) 40.1 (15 to 111.9) 8.1 (2.3 to 29.2)	1.4 (0.5 to 4.3) 1.1 (0.4 to 3.1) 2.3 (0.9 to 5.9) 6.8 (2.5 to 18.5) 21.6 (7.7 to 60.7) 7 (1.9 to 25.7)
Extracranial Injury	ISS 1 unit increase	1.02 (1.00 to 1.04)	1.03 (1.002 to 1.05)
Age	Year 1 unit increase	1.01 (1.006 to 1.015)	*
Sex	Female	1.04 (0.83 to 1.31)	*
Intoxicated	Yes	0.98 (0.77 to 1.24)	*
Seizure pre-hospital or in ED	Yes	1.2 (0.7 to 2)	*
Vomit pre-hospital or in ED	Yes	1.3 (1 to 1.7)	*
Initial Blood pressure	1 unit increase, Mean Arterial Pressure mmHG	1.004 (1 to 1.01)	*
Initial Oxygen Saturation	% (1 unit increase)	0.99 (0.95 to 1.04)	*
Initial Respiratory Rate	RR per Min (1 unit increase)	1.05 (1.02 to 1.08)	*
Platelet Value	10^9/L (1 unit increase)	1 (0.997 to 1)	*
Skull Fracture (Simple)	Yes	1.1 (0.8 to 1.4)	*
Skull Fracture (Complex)	Yes	0.955 (0.7 to 1.2)	*
Contusion Present	Yes	1.4 (1.1 to 1.7)	*
Extradural bleed	Yes	2 (1.4 to 2.9)	*
Intraparenchymal haemorrhage Present	Yes	1.2 (0.9 to 1.6)	*
Subdural bleed	Yes	2.2 (1.8 to 2.8)	*
Intra-ventricular bleed	Yes	1.9 (1.81to 3.4)	*
Subarachnoid bleed	Yes	1.4 (1.1 to 1.7)	*
Comorbidity	Charlson Index	1.07 (1.03 to 1.11)	*
Rockwood Frailty Score Vs under 50	CFS 1-3 CFS 4-6 CFS 7-9	1.3 (1.04 to 1.7) 1.6 (1.2 to 2.2) 2.8 (1.7 to 4.6)	*

* Not selected into model

Table 6.3: Candidate factor (uni and multi-variable) association with neurosurgical admission

Candidate Factor	**Category**	**Univariable effect on risk of deterioration : Odds ratio (95% CI)**	**Multivariable effect on risk of deterioration: Odds Ratio (95% CI)**	
Age	Year (1 unit increase)	0.99 (0.99 to 1)	$(Age/10)^3$ Fractional Polynomial	0.997 (0.996 to 0.9989
GCS Vs 15	GCS14 GCS13	2 (1.5 to 2.8) 3.8 (2.6 to 5.7)	2.3 (1.6 to 3.3) 3.7 (2.3 to 5.9)	
Abnormal Neurological Examination	Abnormal	2.4 (1.7 to 3.4)	1.9 (1.3 to 3)	
Haemoglobin	Grams/litre (1 unit increase)	1 (0.99 to 1.01)	0.99 (0.98 to 1)	
Injury severity on CT Vs simple skull fracture (categories described in detail supplementary material 2)	2) Complex Skull fractures 3)1-2 bleeds < 5mm (total) 4) No or minimal mass effect 5) Significant midline shift 6) High/mixed-density lesion 7) Cerebellar/Brain stem injury	1.9 (0.4 to 9.6) 1 (0.2 to 4.8) 3.3 (0.8 to 13.6) 11.5 (2.7 to 49) 41.7 (9.8 to 178) 8 (1.3 to 47.6)	0.9 (0.5 to 4.9) 0.8 (0.1 to 4.1) 2.3 (0.5 to 9.7) 7.4 (1.6 to 33.9) 37.1 (8.1 to 169) 8.5 (1.3 to 56.2)	
Skull Fracture (Complex)	Yes	1.7 (1.3 to 2.3)	2 (1.3 to 3)	
Subdural bleed	Yes	2.2 (1.6 to 2.9)	1.7 (1.2 to 2.5)	
Extracranial Injury	ISS (1 unit increase)	1.03 (1.004 to 1.06)	1.06 (1.03 to 1.09)	
Rockwood Frailty Score Vs under 50	CFS 1-3 CFS 4-6 CFS 7-9	1.2 (0.9 to 1.6) 0.4 (0.2 to 0.7) 0.09 (0.01 to 0.6)	1.9 (1.1 to 3.1) 0.7 (0.3 to 1.8) 0.09 (: 0.01 to 0.7)	
Sex	Female	0.66 (0.48 to 0.91)	*	
Preinjury anti-coagulation or anti-platelets	Yes	0.95 (0.7 to 1.3)	*	
Intoxicated	Yes	1.1 (0.8 to 1.5)	*	
Seizure pre-hospital or in ED	Yes	1.8 (0.99 to 3.18)	*	
Vomit pre-hospital or in ED	Yes	1.5 (1.1 to 2.1)	*	
Initial Blood pressure	1 unit increase, Mean Arterial Pressure mmHG	1.006 (1 to 1.01)	*	
Initial Oxygen Saturation	% (1 unit increase)	1 (0.94 to 1.07)	*	
Initial Respiratory Rate	RR per Min (1 unit increase)	1 (0.99 to 1.07)	*	
Platelet Value	10^9/L (1 unit increase)	0.99 (0.998 to 1.001)	*	
Number of Injuries on CT Vs 1	2 3 4 5 Diffuse injury	1.4 (0.98 to 2.1) 1.5 (1 to 2.4) 3.4 (2.2 to 5.3) 4.3 (2.7 to 7) 1.8 (0.4 to 8.3)	*	
Skull Fracture (Simple)	Yes	1.2 (0.8 to 1.7)	*	
Contusion Present	Yes	1.3 (0.997 to 1.8)	*	
Extradural bleed	Yes	2.6 (1.7 to 3.9)	*	
Intraparenchymal haemorrhage Present	Yes	0.7 (0.5 to 1.2)	*	
Intra-ventricular bleed	Yes	0.7 (0.3 to 1.9)	*	
Subarachnoid bleed	Yes	1.4 (1 to 1.9)	*	
Comorbidity	Charlson Index (1 unit increase)	0.94 (0.89 to 1)	*	

*Not Selected into model

Model Performance

Table 6.4 summarises measures of model performance. The models predicting the primary and secondary outcomes had Briers scores of 0.16 and 0.09 respectively. The model predicting composite deterioration (primary outcome) had an optimism-adjusted C-statistic of 0.75 and the model predicting need for specialist neurosurgical admission had an optimism-adjusted C-statistic of 0.85. The trade-off between the sensitivity and specificity of these models is shown in the ROC curves in Appendix 33.

Table 6.4: Performance of predictive models

Outcome	**Measure**	**Apparent Performance**	**Average Optimism**	**Optimism Adjusted**
Clinical Deterioration	Brier Score	0.16		
	Calibration Slope	1	0.14	0.86
	C-statistic	0.773	0.026	0.747
Need for specialist neurosurgical admission	Brier Score	0.09		
	Calibration Slope	1	0.04	0.96
	C-statistic	0.86	0.01	0.85

The mild TBI Risk Score

Table 6.5 presents the weighted risk score derived from our prognostic model predicting deterioration. Haemoglobin, although a statistically significant predictor in multivariable modelling was not included as, due to the small effect size and range of abnormal values, inclusion did not improve performance (Appendix 34). Based on the trade-off between sensitivity and specificity, a patient risk score of 0 was used as a threshold for ED discharge. Patients as this cut off had the following characteristics: initial GCS15, single simple skull fracture or haemorrhage<5mm, up to 2 extra-cranial bony or organ injuries not requiring hospital admission, not anticoagulated/taking antiplatelets, no cerebellar/brain stem injuries, and normal neurological examination (Table 6.5). Patients

with a risk score of 1-5 had a 17.5% risk of deterioration and patients with a risk score >5 had 54% risk of deterioration (Appendix 35)

Table 6.5: Mild TBI Risk score

Factor	**Coefficient (optimism adjusted)**	**Risk Score Value**
Preinjury Anti-coagulation or anti-platelets	0.3	1
GCS 15 14 13	0 (Vs) 0.4 0.7	 **GCS 15** 0 **GCS 14** 1 **GCS 13** 2
Normal first Neurological Examination	0.45	**Abnormal** 1.5
Number of Injuries on CT **1** **2** **3** **4** **5** **Diffuse**	0 (Vs) 0.25 0.4 0.8 0.9 0.3	 **1** 0 **2** 1 **3** 1 **4** 3 **5** 3 **Diffuse** 1
Injury severity on CT* **1** simple skull fracture **2** complex Skull Fracture **3** 1-2 bleeds < 5mm **4** No or minimal mass effect **5** Significant midline shift **6** High/mixed-density lesion **7** Cerebellar/Brain stem injury	0 (Vs) 0.3 0.08 0.7 1.7 2.7 1.7	 **1** 0 **2** 1 **3** 0 **4** 2 **5** 5 **6** 9 **7** 5
ISS (body regions excluding head)	0.2	**Up to 2 non-significant extra-cranial injuries**** 0 **Any significant extra-cranial injury or 3 or more injuries** 2
Hb	-0.01	Not included in risk score
Constant	-1.38	

*TBI severity categories are described in detail in Supplementary material 2

** Injuries exclude superficial lacerations and abrasions and a significant extra-cranial injury is defined as any injury requiring inpatient care

The performance of the BIG criteria and our risk score were assessed in the 1569 patients with complete data for both classification systems. A threshold of 0 in our risk score achieved a sensitivity of 99.5% (95% CI: 98.1% to 99.9%) and specificity of 7.4% (95% CI: 6% to 9.1%) to the primary outcome. The BIG criteria for discharge achieved the same sensitivity for deterioration but lower specificity (Table 6.6). Table 6.6 summarises the characteristics of the false negatives (patients meeting the discharge threshold who

deteriorated) in both approaches. No patients recommended for discharge by either criteria, died or required neurosurgery, but 1 patient recommended for discharge by the BIG criteria required intubation. The BIG criteria would have allowed discharge of 57 patients (3.6%) compared to 87 patients (5.5%) with our risk score.

Table 6.6: Performance of mTBI risk score and BIG criteria

N=1569	**Deteriorated**	**Didn't deteriorate**	**Positive Predictive Value (PPV)** **Negative Predictive Value (NPV)**
Performance of Risk score			
Admission (Score>0)	423	1059	PPV = 28.5%
Discharge (Score=≤0)	2*	85	NPV = 97.7%
	Sensitivity= 99.5% (95% CI: 98.1% to 99.9%)	Specificity= 7.4% (95% CI: 6% to 9.1%)	
Performance of BIG criteria			
Admit (not BIG1)	423	1089	PPV = 28%
Discharge (BIG 1)	2*	55	NPV = 96.5%
	Sensitivity = 99.5% (95% CI: 98.1% to 99.9%)	Specificity= 4.8% (95% CI: 3.7% to 6.3%)	

*Patients recommended for discharge by our risk score who deteriorated:
1) 85 female, small subdural dropped GCS. Rockwood frailty score 4.
2) 56 male, small contusion (report stated possible 2nd small intra-cranial haemorrhage, only first injury included) and pre-injury seizure. Seizure during admission.

Patients triaged to discharge by BIG who deteriorated:
1) 85 female, small subdural dropped GCS. Rockwood frailty score 4.
2) 55 female, small subdural and poly trauma (ISS 10). Required intubation.

Discussion

Summary

To our knowledge, this is the first UK study to report the risk of deterioration in all initial mild TBI patients with traumatic injuries reported on CT brain scan and study internationally to develop a prognostic model and risk tool for avoiding unnecessary hospital admissions. We also report the first independent validation of the BIG criteria.

The estimated prevalence of deterioration was 27.7%. Our prognostic models for composite measures of deterioration had optimism adjusted C statistics of 0.75 and 0.85, indicating good discrimination between patients with and without deterioration or need for neurosurgical care.

Using our risk score, derived from the prognostic model, to hypothetically direct need for hospital admissions, it would appear safe to discharge from the Emergency Department patients who are fully conscious with no focal neurology (GCS15) – not taking anticoagulant or antiplatelet medication, who have with a single simple skull fracture or haemorrhage <5mm (not cerebellar or brainstem) on CT brain scan and up to two extra-cranial bony or organ injuries not requiring hospital admission (risk score 0). This derived decision rule, achieved a sensitivity of 99.5% and specificity of 7.4% for deterioration. Categorisation of patients for discharge using the BIG criteria achieved the same sensitivity but a lower specificity.

The model predicting need for neurosurgical admission (based on risk of an interventional outcome) found higher age and frailty reduces risk. This probably reflects clinical selection of patients, with frail older patients less likely to undergo invasive interventions.

Strengths

We believe this is the largest multi-centre cohort study undertaken to estimate the prevalence of a composite measure of deterioration in this population.[28] The study was powered to develop a prognostic model predicting this outcome. Candidate predictor factors were selected a priori on the basis of existing literature.[33] We followed established techniques for handling missing data, prognostic modelling and adjusting for optimism.[41, 236, 239, 246]

Limitations

Due to the resource implications of conducting a prospective study we pragmatically chose a retrospective study design. Around 25% of patients had missing data, but as these

data were mainly missing through poor recording or missing notes, and therefore missing at random, imputation techniques were valid. Documentation inaccuracies may have introduced random error, but are unlikely to have introduced systematic bias.

We classified TBI severity using information in written CT reports by using AIS coding to map to a modified Marshall classification. Poor reporting of the size of injuries and extent of mass effect meant most injuries were classified as equivalent to Marshall classification II. Better systematic and standardised reporting may have allowed TBI severity to be better classified and improved the performance of the derived models.

Outcomes were limited to those recorded in hospital records, which may mean that patient deterioration in the community was missed. However, this is unlikely and a check in Hull of deaths recorded in patients eligible for entry on the national trauma registry (linked to office of national statistic mortality reporting) found no missed deaths.
We only assessed the predictive value of routinely collected factors. We could not assess the potential predictive value of using non-routinely collected variables identified in our review[6] or biomarkers.

Although we have internally validated our derived models, they have not been externally validated. There is debate about the best way to combine imputation of missing data and internal validation bootstrapping techniques.[244] We chose to bootstrap within imputations due to lower computational complexity. This has been shown in simulation studies to provide accurate estimates of the shrinkage factor.[244] Other studies[247] found imputing within bootstraps better adjusts for optimism and therefore despite adjusting for overfitting, our models may perform less well when applied to new data.

The lower prevalence than expected of the secondary outcome means our study may not be adequately powered to derive a model accurately predicting this outcome.

Comparison Previous literature

The estimated prevalence of clinical deterioration at 27.7% was higher than previously reported. In our review we found the pooled prevalence of clinical deterioration to be around 10%.[28] This reflects differences in study design; previous studies used narrower outcome definitions, such as neurological deterioration or ICU intervention,[28] whilst we used a wide composite primary outcome aimed at encompassing need for hospital admission. We assessed an unselected GCS13-15 population, whilst previous studies often restricted their inclusion criteria on the basis of GCS scores, injury severity, admitting inpatient specialty and medication use.[6]

Research assessing prognostic factors in this TBI population have frequently used sample sizes based on convenience and lacked the statistical power to assess potential predictors simultaneously.[27, 28] Our study was sufficiently powered to assess over 40 candidate variables in multivariable modelling. Previous research found initial GCS, type of brain injury, anti-coagulation and age were the strongest predictors of adverse outcomes in this population.[28] In our multivariable model all these factors were also found to be predictors of deterioration.

Studies evaluating the BIG criteria in the Level 1 trauma centre in the USA, where it is routinely applied, found around 10% of patients met the criteria for ED discharge and no patient that met these criteria had adverse outcomes.[31, 248] In our cohort 4% of patients met the criteria for ED discharge and two of these patients deteriorated. Our study cohort was on average older and had a lower GCS than studies previously assessing the BIG criteria, which may account for the difference in performance.

Implications

Between April 2014 and June 2015 around 11, 000 TBI patients were admitted to specialist neurosurgical centres in the UK and over 50% of these patients had mTBI.[8] Currently all patients with TBI identified by CT imaging are admitted to hospital. Consequently, any risk stratification tool which could safely reduce unnecessary

admissions may save significant health service resources. Internationally, and particularly in the USA, there is wide variation in admission practices in this group with a range of specialist admission and discharge criteria used on the basis of limited evidence.[30, 31, 157, 178] Accurate risk prediction has the potential to help rationalise admission decisions in this group.

Our risk tool demonstrated good predictive accuracy (99.5% sensitivity to our primary outcome) at the proposed threshold for ED discharge. This would have allowed the discharge of 87/1569 patients (5.5%). A negative predictive value of 97.7% was achieved (about a 1 in 50 chance of a discharged patient deteriorating). This may not be clinically acceptable, but no patient recommended by our risk score for discharge died, required neurosurgery or an ICU intervention. One patient recommended for discharge had a report indicating a possible second lesion, and therefore may have been admitted in clinical practice. The BIG criteria achieved the same sensitivity (99.5%) to the primary outcome but its lower specificity means clinical application would result in fewer patients being discharged.

The high predictive accuracy of our model for the secondary outcome (AUC = 0.85) suggests it could be used to triage neurosurgical admissions in this population. The acceptable level of risk of requiring invasive intervention for a patient admitted under a non-specialist team is unknown and is likely to vary between centres. The lower prevalence of this outcome means the estimated model may be less accurate and we regard this as a starting point for further research.

Both our prognostic model and the BIG criteria should be validated prospectively before they could be used in clinical practice. A prospective study design would address the weaknesses in outcome collection highlighted earlier and allow the inclusion of non-routinely collected prognostic factors including biomarkers. Improved systematic reporting of CT scans could possibly increase the predictive accuracy of our model and further increase the performance of our risk tool.[232, 249] Economic evaluation is also required to comprehensively assess the implication for both patient outcomes and resource use of using the model.

Conclusion

This is the first study to empirically derive a prognostic model for patients with mTBI and injuries identified by CT imaging and independently validate the BIG criteria. Our empirically derived risk tool performed better than the BIG criteria and could be used to safely discharge from the ED one in twenty patients currently routinely admitted for observation. Both our prognostic model and the BIG criteria now require prospective external validation and economic evaluation.

Chapter 7: Discussion

Summary

This thesis presents research which investigates two broad research questions:

1) What impact have national head injury guidelines in Scotland and England had on hospital admission and TBI mortality rates?

2) Is it possible to develop a prognostic model for GCS13-15 TBI patients which can identify patients who can be safely discharged from the ED?

These research questions were addressed by the following aims:

1. Assess the impact of national head injury guidelines on:
    - Population based inpatient traumatic brain injury mortality rates
    - Population based admission rates for head injury and traumatic brain injury

2. Develop a prognostic model to accurately predict risk of deterioration in alert patients, with traumatic abnormalities on CT head scan, which could be used to refine the guidelines.

This chapter summarises and discusses the research addressing the two research questions separately and in the final part of this chapter presents an overview of all the completed research and its implications.

Part 1: Evaluation of Head Injury Guidelines

Part 1 of this thesis used complete national NHS data sets for Scotland and England and interrupted time series analysis to address the first research question and aim. This is the first time that complete national data sets and robust quasi experimental techniques

have been used to evaluate the impact of clinical head injury guidelines on hospital admissions and deaths internationally. The key findings are summarised in table 7.1.

Analysis of the Scottish data found admissions for head injury fell overall from around 40 per 100 000 population to around 30 per 100 000 population, with a reduction in admissions associated with the introduction of each SIGN guideline. However, the impact of the guidelines on admissions for head injury varied greatly by age group and an increase in admissions for patients with ICD 10 codes indicating radiologically diagnosed TBI was observed. The trends in admissions and mortality for TBI in England also differed greatly by age group. A NICE guideline associated reduction in the admitted TBI population mortality rate was only observed in the 16-64 age group.

Table 7.1: Summary of Interrupted Time Series Analyses results

All ages		
Study outcome	**Scottish data**	**English data**
Population based head injury admission rates	Both guidelines associated with significant reduction in trends in head injury admissions – after first guideline this appeared undermined by 4-Hour target	Not assessed
Population based radiologically diagnosed TBI admission rates	Significant increased trend admission rates associated with both SIGN guidelines.	Not assessed
Population based radiologically diagnosed inpatient TBI mortality rates	No change to secular trend of increasing TBI population mortality rate Significant downward trend proportion admitted TBI population died all causes at 30 days following admission associated with second SIGN guideline	Not assessed
65+ Age Group		
Study outcome	**Scottish data**	**English data**
Population based head injury admission rates	Secular trend of increasing admission rate not impacted by guidelines	Not assessed
Population based TBI admission rates	Not assessed	1st guideline associated with increased admissions (4- Hour Target contemporaneous)

		Reduction and levelling off of admission rate associated with 2nd and 3rd NICE guidelines
Population based inpatient TBI mortality rates	Not assessed	Secular trend of increasing mortality unaffected by the introduction of the guidelines.
16-64 Age Group		
Study outcome	**Scottish data**	**English data**
Population based head injury admission rates	Significant reductions in trend of admissions associated with both SIGN guidelines Reductions appeared counteracted by 4-Hour target	Not assessed
Population based TBI admission rates	Not assessed	Significant increase trend associated 1st NICE guideline (4-Hour Target contemporaneous) Reductions trend associated 2nd guideline
Population based inpatient TBI mortality rates	Not assessed	Significant reversal of increasing mortality trend after 2nd guideline
0-15 Age Group		
Study outcome	**Scottish data**	**English data**
Population based head injury admission rates	Secular trend of reduction in admissions unaffected by SIGN guidelines or 4-hour target	Not assessed
Population based TBI admission rates	Not assessed	Secular trend of reduction in admissions unaffected by NICE guidelines
Population based inpatient TBI mortality rates	Not assessed	Secular trend of reduction in mortality rate unaffected by NICE guidelines

The impact of head injury guidelines on hospital admissions and deaths

The population of patients used for the evaluation of the impact of the SIGN and NICE guidelines on admissions in England and Scotland differs slightly. The Scottish data assessed admissions for patients with ICD10 codes indicating any type of head trauma and this was used to evaluate the impact of the SIGN guidelines on admissions for patients presenting with head injury. This population was selected to specifically assess

whether guideline recommended increased CT imaging led to predicted reductions in hospital admissions for patients with head injury. This analysis was completed using Scottish data as the SIGN guidelines were introduced at a different time to the 4-hour target.

The analysis of admissions in England used ICD10 codes indicating admission for TBI, as this included codes for concussion and other types of minor TBI, these ICD10 codes are identical to those used in the Scottish analysis but with codes for superficial injuries excluded. This population was selected to assess whether the guidelines had improved outcomes for patients with diagnosed TBI. The impact of national head injury guidelines on deaths due to TBI was evaluated using English data as the individual level Office of National Statistics linked Hospital Episode Statistics extract allowed deaths attributable to TBI to be identified and adjusted for changes in population characteristics. Superficial injuries were excluded as they were not plausibly life-threatening. As discussed in Chapter 3, the death rate was assessed at a population level as ED attendance data was unavailable and the guidelines plausibly affected both deaths and inpatient admissions.

The observed effects associated with the introduction of guidelines and the 4-hour target varied greatly by age group (Table 7.1).

≥65 Age Group:

In the 65+ age, hospital admissions for head injury in Scotland almost doubled from 1998 to 2016, with the monthly rate of admissions increasing from around 40 per 100, 000 to just under 80 per 100, 000. In England, monthly hospital admissions for TBI in this age group increased from 10 per 100, 000 to around 30 per 100, 000. So, there were similar trends in head injury and TBI admissions in this age group in both countries. The higher estimated admission rates in Scotland probably reflects the broader range of ICD10 codes used to define head injury, compared to TBI in the English data. The introduction of the first SIGN guideline in Scotland was associated with a non-statistically significant reduction in trend of the hospital admissions in this age group (Table 2.3: -0.16; 95% CI: -0.40 to 0.09). The introduction of the 4-hour target reversed this and was associated with

an increasing rate of admissions (0.15; 95% CI: 0.01 to 0.28) and this was unaffected by the introduction of the 2nd SIGN guideline (Table 2.3).

In England there was a large increase in level (1.71; 95% CI:-0.01 to 3.44*)* and trend (3.3: 0.17; 95% CI: 0.11 to 0.23) of hospital admissions for TBI at the time of the introduction of the first NICE head injury guideline, concurrent with the introduction of the 4-hour target (Table 3.3). This increase in TBI admissions, it has been argued, may result from increased case ascertainment of TBI. The guidelines include more recommendations for CT imaging in those 65+ than in younger adults, and prior to the guidelines this age group were less likely to be imaged in the ED, probably leading to admission coding being attributed to reasons unrelated to head trauma.[8, 56] The subsequent two NICE guidelines were associated with a reduction and ultimate levelling off in the rate at which hospital admissions for TBI increased.

In England, the monthly admitted population TBI mortality rate for those aged 65+ trebled between 1998 and 2017 from 0.5 per 100, 000 to over 1.5 per 100, 000. This was unaffected by any of the NICE guidelines. Sub-group analysis of those aged 65-84 and those 85+ showed that this trend was the same in both age categories but that there was greater increase in TBI mortality in those aged 85+ with an increase in the monthly death rate from around 0.5 per 100, 000 to over 6 per 100, 000. As with the whole 65+ age group, there were no significant changes in level or trend associated with the introduction of any NICE guideline in either the 65-84 or 85+ age sub-groups.

16-64 Age Group:

In the 16-64 age group, monthly hospital admissions in Scotland for head injury fell from around 35 per 100, 000 to around 20 per 100, 000 over the study period. In England monthly hospital admissions for TBI also decreased from around 30 per 100, 000 population to around 20 per 100, 000 across the same period. In Scotland, the first SIGN guideline was associated with a significant reduction in the trend (-0.20; 95% CI: -0.35 to -0.05) (Table 2.3).

In both Scotland and England, the introduction of the 4-hour target (which coincided with the introduction of the first NICE guideline in England) is associated in a reversal in the existing downward trends in hospital admission for head injury and TBI and an increase in hospital admissions over time. As discussed in Chapter 2, the increase in admissions associated with the 4-hour target may reflect difficulties in recommended imaging being completed in the ED within the constraints of the 4-hour target, leading to admissions solely for the purposes of imaging. The introduction of the 2nd SIGN and NICE guidelines, both of which advocated a more rapid used of CT imaging (within a 4-hour limit), were both associated with a return to the downward trend in hospital admissions which predated the introduction of the 4-hour target.

In England, only the second NICE guideline was associated with a reduction in the admitted TBI mortality rate and only in the 16-64 age group (Fig. 3.1). This reduction reversed the underlying secular trend of increasing TBI mortality. I found no other changes in mortality associated with any of the other three guideline iterations in either the paediatric or 65+ age group. The introduction of the second SIGN guideline (which like the second NICE guideline recommended that patients with severe injuries are managed in specialist centres) was also associated with a statistically significant reduction in the proportion of patients of all age groups admitted with TBI identified radiologically in Scotland who died. This reduction in the proportion of admitted TBI deaths may reflect an increase in the number of admissions (denominator) and an associated reduction in injury severity as increased CT imaging led to a greater number of less severe injuries being identified. The reduction in deaths attributable to TBI in England may also reflect a reduction in the incidence of serious TBI occurring in this age group due to prevention initiatives such as road safety. There was no evidence of a reduction in mortality associated with the introduction of 4-hour target in either England or Scotland in the 16-64 or any other age group.

0-15 Age Group:

In the 0-15 age group there was a continuous downward trend in hospital admissions for head injury in Scotland and TBI in England which was unaffected by the introduction of

any guideline. In Scotland, hospital admissions for head injury halved from around 50 per 100, 000 per month to around 25 per 100, 000 per month between 1998 and 2016 and in England monthly admissions for TBI more than halved, from 20 per 100, 000 per month to under 10 per 100, 000 between 1998 and 2017.

In the 0-15 age group the mortality rate fell continuously in England over the time period from around 0.05 to 0.01 per 100 000 population. None of the guidelines were associated with a statistically significant change in the level or trend in the mortality rate.

Inpatient hospital admissions for Traumatic Brain Injury on CT scan:

To specifically assess whether increased CT imaging has caused an unintended increase in hospital admissions for patients with minor injuries identified radiologically, the impact of the SIGN guidelines on monthly admissions in Scotland for patients of all age groups with a subset of ICD10 codes indicating radiological diagnosis of TBI was assessed. Admission for this group increased in Scotland from around 6 per 100, 000 population to over 10 per 100, 000 population over the study period. The introduction of both SIGN guidelines was associated with statistically significant increases in trend of admissions for this group and the 2nd SIGN guideline had the largest associated increase. There was also a statistically significant reduction in the proportion of such admissions which resulted in neurosurgery associated with the introduction of each guideline, indicating that the additional admissions may have had a higher proportion of patients with lower severity injuries. This was part of the motivation for the second part of the research presented in this thesis.

Strengths

This thesis presents the first national evaluation using interrupted time series analysis of the impact of the NICE and SIGN head injury guidelines. The analysis uses the different times at which the guidelines were implemented in Scotland and England to explore the effect of the introduction of the 4-hour target, a potential co-intervention. NHS administrative data is collected at all hospitals in England and Scotland and this allowed evaluation of the impact of head injury guidelines at a national level. Evaluations which

have been undertaken previously utilised evidence from single centre studies or subsets of patients.[24, 72, 73]

There is debate regarding which ICD10 codes correspond to clinical definitions of head injury and TBI with inconsistent sets of ICD10 codes used to encompass both.[51] I used different coding groups to evaluate different aspects of guideline implementation. I selected a wide range of ICD 10 codes to define head injury that are likely to be sensitive to changes in admission practice related to increased diagnostic precision of TBI from increased CT imaging (Table 2.1). Admissions for patients with these ICD10 codes are also likely to be sensitive to increases related to meeting the 4-hour target, where imaging was not possible within 4-hours in the ED. This allowed me to assess whether the introduction of head injury guidelines achieved intended reductions in hospital admissions for head injury.

An ICD10 code subset was used to define radiologically detected injuries to order assess the effect of increased diagnoses of TBI by CT imaging. When evaluating the impact of the NICE guidelines on TBI mortality validated Centres for Disease Prevention and Control ICD9 and 10 code definitions were used to identify deaths attributable to TBI, consistent with previously conducted research.[64]

Established statistical techniques were used when conducting the interrupted time series analyses with adjustment for seasonal effects and other forms of auto-correlation.[38] Adjustment was made for changes in population demographics using ONS mid-year population estimates for analysis of guideline effects on hospital admissions. Additionally, adjustment using individual level inpatient data was made in the evaluation of the impact of the NICE guidelines on TBI mortality. Sensitivity analyses were completed to look for the effects of implementation lags, changes in population demographics and changes in diagnostic coding; these indicated that the results were robust (Appendices: 7, 10, 13, 18, 19, 20 and 36).

Weaknesses

There were significant challenges and delays in obtaining individual level Hospital Episode Statistics data from NHS digital. Therefore, aggregate level Scottish data was obtained and analysed first, before analysing individual level HES data. If equivalent individual level Scottish data had been available, as the NICE and SIGN head injury guidelines were introduced at different times, it may have been possible to conduct a Difference in Differences analysis to directly compare trends in identical outcomes.[250] This would have represented a further robust method to assess causal effects associated with the introduction of the head injury guidelines. The differences in the Scottish and English data sets that were available prevented this analysis.

The impact of the NICE and SIGN guidelines on inpatient TBI mortality and head injury admissions were evaluated at a population level, meaning that rates were calculated using mid-year population estimates. This represented the best available unbiased measure of mortality and admission rates. However, these outcomes may have been affected by changes in the underlying population head injury rates and resultant TBI rates. If changes in the underlying rate occurred around the time of guideline introduction, this might affect the interpretation of the estimated guideline effect. However, as discussed in Chapter 3, the available ED HES data showed annual attendances to the ED for head injury gradually and smoothly increased over the study period and are unlikely to explain the sharp discontinuity associated with the introduction of the second NICE guideline (Figure 3.1). Ideally, both the hospital admission rates and TBI morality rates would have been estimated using ED attendance for head injury and TBI as the denominator. This would have better captured the impact of the guidelines on the population at risk and allowed adjustment for step or non-linear changes in ED attendance. ED data however were not collected until 2007 in England and were initially of poor quality and only collected by a subset of hospitals, so preventing this analysis. The impact of the NICE guidelines on TBI mortality in those admitted with TBI in England could be estimated, but because the guidelines resulted in changes in admissions policies and rates, the rate of deaths per admission is difficult to interpret.

The limitations of data routinely collected for Hospital Episode Statistics in England meant that mortality rates could only be adjusted for age, comorbidity and gender. Adjustment

for other known predictors of TBI mortality including anatomical severity of brain injury, GCS neurological examination findings and presenting physiology was not possible, as they were not collected.[86] However, adjustment for the available predictors of TBI mortality did not materially change estimates associated with the introduction of the guidelines and no evidence was found to indicate that the prevalence of these additional factors changed at the point individual guidelines were introduced.

Each guideline contains multiple recommendations regarding indications and timing for CT imaging and the clinical management TBI. I attributed the reduction in inpatient mortality rates observed in England in the 16-64 age group (associated with the introduction of the second NICE head Injury guideline) to increased management of patients with severe TBI in specialist centres. This is supported by previous studies which found a mortality benefit from management of severe TBI in specialist centres and an increase in such specialist care around the time of the second guideline which specifically recommended this.[21, 23] However, the second NICE guideline included a range of additional new recommendations, including that CT imaging for high risk minor head injured patients should be requested immediately in the ED.[12] It is plausible that faster imaging and subsequent diagnosis of life-threatening TBI also contributed to the observed reduction in TBI mortality.

Administrative data sets, such as HES and ISD data, are not generated for the purpose of research and often contain inaccuracies due to poor coding.[53] Random poor coding is unlikely to account for discontinuities observed at the specific time points of interest, but the "noise" they produce may make a discontinuities harder to detect. Systematic changes in coding practice, or the population data on whom the data is collected, at specific time points can confound interrupted time series analysis. However, there were no changes in inclusion criteria for the administrative datasets relevant to this study during the study period in either Scotland or England. ISD data have been found to be both sufficiently reliable and comprehensively collected to support its use in research.[54, 55] ICD10 coding was used consistently for HES and ISD data collection throughout the study period. ONS changed from ICD9 to ICD10 coding of cause of death in 2001. However, a sensitivity analysis excluding the period before 2001 did not materially alter

the estimates associated with the introduction of the NICE guidelines in England (Appendix 36).

Clinical Decision Units (CDUs) are Emergency Department run clinical areas, ranging from inpatient ward care to ambulatory units, where patients can be observed for a short period of time and await the results of investigations.[251] It has been argued that the use and number of CDUs may have increased in response to the introduction of the 4-hour target in the UK.[251] Clinical Decision Unit admissions were not differentiated from other types of inpatient admissions in either the Scottish or English data sets. Admission to such units may have fewer resource implications than traditional inpatient admissions and may have been used for patients awaiting guideline recommended CT imaging when it was not possible within the constraints of the 4-hour target. Therefore, the resource impact of increased hospital admissions associated with the introduction 4-hour target may be less than described. However, the extent to which Clinical Decision Unit admissions in the UK represent materially different and more cost-effective care compared to other types of hospital admissions and should be treated differently is debatable.[57] Furthermore, only 6 hospitals in Scotland had Clinical Decision Units during the time period of the interrupted time series analysis reported in Chapter 3 and they were not established at the same time the SIGN guidelines or 4-hour target were introduced.[58]

Comparison to previous literature

Changes in yearly trends in hospital admissions for TBI in Scotland in the period 1998-2009 have previously been identified using the same ISD data set used in this thesis but in a population identified with slightly different ICD10 codes.[42] Like the study presented in Chapter 2, Shivaji et al found increases in TBI admissions in those 65+, particularly from 2004 after the introduction of the 4-hour target, and decreases in admissions in those 0-15 over their study period. The study reported in Chapter 2 additionally found reductions in hospital admissions in those 16-64 in the period after the introduction of the 1st SIGN guideline in 2000, which reversed after the introduction of the 4-hour target in 2004. Unlike the analysis presented in chapter 2, Shivaji et al did not look for discontinuities at time points corresponding to the introduction of health policies, but instead estimated models to fit the data and assessed for time points where the models changed.[42] Their use of annual instead of monthly rates also meant their study was poorly powered to establish underlying trends.[42] The analysis did not consider the possible impact of the SIGN guidelines or 4-hour target on TBI admissions during this period. No other relevant studies assessing national trends in head injury or TBI admissions in Scotland in the time period following the introduction of the SIGN guidelines were found.

Previous studies evaluating the impact of the NICE head injury guidelines have either used TARN data, [13] which is collected on a subset of more severely injured TBI patients who meet specific inclusion criteria, or have been conducted at single sites.[15, 23, 43, 252, 253] Such evaluations have been limited to assessing the impact of either the first or second guideline and none used interrupted time series analysis or other robust quasi-experimental methods. Two previous studies have assessed annual trends in hospital admissions for head injury in England using HES data.[18, 59] One of these studies also reported annual trends in deaths in paediatric patients admitted with head injury.[59] Both studies assessed time periods which did not include the introduction of all three guidelines. The research presented in this thesis represents the first national evaluation of the impact of all three NICE head injury guidelines using a quasi-experimental method. This is the first joint analysis of Scottish and English data to evaluate the impact of the 4-

hour target on hospital admissions for head injury and TBI contemporaneously with guideline introduction.

An NIHR Health Technology Assessment of clinical decision rule use, assessing which minor head injured patients require CT imaging, found that the use of Canadian CT Head based decision rules on which NICE guideline recommendations are based is cost effective.[16] This was based partly on findings of early implementation studies of the first NICE guideline and a Swedish randomised control trial.[15, 17, 43] These studies found costs of increased CT imaging would be offset by a reduction in hospital admissions. However, analysis of HES data found that annual admissions for head injury actually increased in England following the introduction of the first NICE guideline.[18] Goodacre hypothesised this may be because of the introduction of the 4-hour target or increased diagnosis of injuries on CT imaging.[18]

In Scotland, where the ED 4-hour target was introduced at a different time to the SIGN guidelines, evidence was found to suggest the 4-hour target acted to undermine reductions in admissions for head injury associated with increased CT imaging. It is therefore likely the 4-hour target contributed to the increase in hospital admissions for TBI and head injury observed immediately after the introduction of first NICE guideline in England. The analysis presented in chapter 2 and 3 shows that later NICE and SIGN guidelines, which recommended more rapid imaging occurring within a timeframe of less than 4-hours in the ED, reversed increases in hospital admissions associated with the introduction of the 4-hour target.

The increase in hospital admissions associated with the introduction of the 4-hour target was much greater in the 65+ age group. In Scotland the second SIGN guideline appeared to have no effect on the trend of increasing admissions for head injury in this group. In England later NICE guidelines appeared to act only to slow the rate of increasing admissions for TBI in this older age group. This implies that guideline-recommended increases in CT imaging of minor head injured patients in this age group may be less effective at reducing hospital admissions than previously reported.[16] Chapter 2 also presents evidence that, as previously hypothesised,[254] increased CT imaging has led to

more admissions across all age groups for patients with TBI identified radiologically, who do not require neurosurgery or die from their injuries. This may be the result of previously unidentified lower severity injuries of uncertain clinical significance now being diagnosed from increased CT imaging and causing additional hospital admissions which undermine intended cost saving from guideline implementation. However, there may be benefits associated with such admissions in the absence of neurosurgery, such as reversal of anti-coagulation, which may make these admissions clinically worthwhile and cost effective. .

A cohort study which used TARN data to assess the impact of the management of patients with severe TBI in specialist centres (recommended by the 2nd NICE guideline) found that the increased rates of treatment of severe TBI patients to specialist centres between 2003-2009 was associated with a halving of severe TBI case fatality.[23] TARN data were collected at approximately half of hospitals in England until 2012 and on a more severely injured TBI patient subset. The research presented in Chapter 3 found that the second NICE guideline, which recommended management of patients with severe injuries in specialist centres alongside more rapid CT imaging, reduced the mortality rate in the 16-64 age group.

A randomised control trial which compared hospital admission for observation to immediate CT imaging in the ED in a subset of minor head injured patients found no mortality benefit from increased immediate CT imaging.[17] Additionally, a mortality benefit associated with treatment of patients with severe TBI in specialist centres has previously been found to be independent of whether patients undergo operative intervention.[21] It therefore seems more plausible that the reduction in mortality associated with the second NICE guideline may result from recommendations regarding specialist care, rather than recommendations for quicker CT imaging in the ED. Patel et al were unable to determine the mechanism for the benefit associated with management in specialist centres in their study.[21] TBI mortality in the those 65+ increased throughout the study period in England and was unaffected by any guideline. The may be due to patients 65+ having reduced access to specialist care as indicated by the TARN older persons audit.[56]

However, this may also reflect treatment in specialist centres being less effective in older patients.[70, 71]

In those aged 0-15, monthly hospital admission rates for head injury declined across the study period in Scotland, as did the rate of TBI deaths and admissions in England. This downward trend was unaffected by any head injury guideline. A paediatric study analysing English HES data from 2000-2011 found a reduction in annual mortality during admissions for head injury after the introduction of 2007 NICE guideline and an increase in head injury admissions from 34 to 37 admissions per 10 000 children.[59] Clinicians have been found to be less likely to implement guidelines which recommended increases in CT imaging in children and this may account for why the introduction of any guideline was not associated with reductions in hospital admissions.[59-61] Differences in study design may be the reason for the contrasting findings in mortality trend. A greater number of data points was used to estimate the time dependent model and ONS-linked HES data to identify deaths directly attributable to TBI.

Interpretation

Part 1 of this thesis attempted to assess the impact national head injury guidelines in Scotland and England had on hospital admission and TBI mortality rates. As admission and mortality rates were assessed at population level the extent to which observed changes can be attributed to the introduction of the guidelines, is dependent on how well the interrupted time series method used was able to control for underlying trends in the population incidence of head injury and resulting TBI. As the mechanism of head injury differs greatly in the three age groups assessed, they need to be considered separately.[3]

In the 65+ age group a large increase in TBI mortality and admissions for head injury and TBI was observed. The only observed significant guideline effect was later NICE guidelines apparently slowing the rate at which TBI admissions increased. As older patients have the greatest number of CT indications in the SIGN and NICE guidelines and have experienced the greatest increase in CT imaging, it possible to attribute some of the observed increases in TBI deaths and admissions to better case ascertainment.[56] The apparent levelling off in TBI admissions observed in England may reflect saturation of diagnosis of a

pre-existing burden of TBI in patients attending hospital in this older age group. Falls are by far the most common mechanism of injury causing TBI in older patients and an "epidemic" of falls in frail older patients has been observed in Europe in the period when the guidelines were introduced.[3, 56] This may have contributed to the observed increasing trends in admissions and deaths. The changes in both the incidence of injury and diagnosis of TBI in older patients may have made guideline associated effects difficult to detect.

The 16-64 age group appeared to show the greatest guideline associated impact with a reduction in overall head injury admissions and TBI mortality. Road traffic accidents are one of the commonest causes of fatal TBI in this age group, and so the guideline associated effects have to be considered alongside improved road safety which almost halved fatalities from road traffic accidents between 2007 and 2017.[3, 255] However, such general improvements in road safety over time are unlikely to cause a reversal in trend of TBI mortality at a discrete time point corresponding to the introduction of the guideline as observed in analysis of English data. As discussed previously, there is additional evidence from research conducted using TARN data to indicate that the introduction of the second NICE guideline reduced TBI mortality in England.[23] Road traffic collisions are a less common cause of head injury presentation and improved road safety is unlikely to have caused reductions in head injury admissions at the discrete time points observed in Scotland.[3] The long period over which changes in trend associated with the introduction of guidelines occurred may reflect that changes to practice required increased CT imaging and specialist management capacity and this required a prolonged time period to fully implement.

The falling admission and TBI death rate observed in the 0-15 population is likely to reflect improved road safety measures and other factors which reduced the incidence of head injury and TBI in this age group.[59] There is evidence to suggest that clinicians have not fully implemented CT imaging recommendation in children due to fears about radiation exposure and this may partly explain why predicted reductions in admissions were not observed.[60]

Part 2: Developing a prognostic model

Summary

The meta-analysis of the literature estimated pooled outcome measures of clinical deterioration as: any clinical deterioration 11.7% (95% CI: 8.21 to 15.8); neurosurgical intervention 3.5% (95% CI: 2.2 to 4.9%); death 1.4% (95% CI: 0.8% to 2.2%). This contrasted to the higher rates of deterioration estimated in the retrospective cohort study presented in Chapter 6: 27.7% (95% CI: 25.5% to 29.9%) clinically important deterioration, 13.1% (95% CI: 11.6% to 14.8%) neurosurgical intervention, ICU admission or intubation and 4.2% (95% CI: 3.4% to 5.3%) death. Where cause of death, ICU admission or readmission was unknown, cause of deterioration was attributed to TBI, which may partly account for the higher estimated deterioration rate in the cohort study presented in chapter 6. However, as discussed later, there were also differences between the cohort study population and the populations of studies included in the review.

Using the prognostic model for the primary outcome of clinical deterioration, a risk score and decision rule was developed which could potentially be used clinically to identify patients who could be discharged safely from the ED. At the proposed risk score threshold for discharge from the ED, a hypothetical sensitivity of 99.5% (95% CI: 98.1% to 99.9%) and specificity of 7.4% (95% CI: 6% to 9.1%) to deterioration would have been achieved, allowing 5.5% of patients to be discharged. The selected predictors of deterioration in the final decision rule are summarised in Table 6.5, those included: preinjury anti-coagulant or anti-platelet use, abnormal neurological examination, number of injuries on CT scan, radiological TBI injury severity and severity of extra-cranial injury.

Categorisation of patients using the BIG criteria from the USA achieved the same sensitivity but a lower specificity (4.8%) and would have allowed only 3.6% of patients to be discharged. No patient recommended for discharge by the derived risk stratification tool or BIG criteria died or required neurosurgery, but one patient recommended for discharge by the BIG criteria required intubation. The studies identified by the review which assessed the BIG criteria found around 10% of patients to be categorised as BIG 1

and therefore recommended for discharge from the ED, none of whom experienced adverse outcomes.[31, 80] However, both these studies were conducted in the centre where the BIG criteria were derived. In the cohort study presented in chapter 6 only 3.6% (n=57) of patients met the criteria for classification as BIG 1 (discharge from the ED) and two of these patients deteriorated.

Strengths

The second part of this thesis presents the first review to provide pooled estimates of clinically important outcomes in GCS13-15 patients with traumatic CT abnormalities and identify which factors affect the risk of these outcomes. The cohort study is the first in a UK ED population to report the risk of deterioration and the first internationally to develop a prognostic model aimed at informing hospital admission decisions. It is also the first study to assess the performance of the BIG criteria in a UK population.

Candidate factors predictive of clinical deterioration were identified in the systematic review using meta-regression to explore between study estimates of deterioration prevalence and pooling of within study prognostic factor effects. 41 candidate factors were identified using these methods with age, initial GCS, type of injury, anti-platelet and anti-coagulant use estimated to be the strongest predictors on pooling. All identified candidate factors, apart from non-routinely collected factors such as venous lactate, were collected and their predictive value assessed in multivariable stepwise logistic regression modelling in the retrospective cohort collected for this thesis.

Unlike many studies identified in the systematic review, the data collected for the prognostic study was on a population of all mTBI patients with injuries identified by CT imaging and did not exclude patients on the basis of their characteristics or clinical treatment. A wide composite measure of deterioration was chosen to encompass need for hospital admission. Candidate factors assessed in the completed cohort study were identified from the systematic review. International guidelines for the conduct and reporting of systematic reviews and prognostic studies were followed.[40, 78] Meta-

regression and pooling of predictive factor effect estimates was used to identify candidate factors in the meta-analysis conducted in conjunction with the systematic review.

The cohort study reported in Chapter 6 was adequately powered to assess all candidate factors identified in the systematic review in multivariable modelling. Established techniques of multiple imputation for handling missing data were used, as was bootstrap internal validation to adjust for optimism in derived models.[78, 256, 257]

To overcome potential variation in data extraction between research team members all staff undertaking data extraction underwent data extraction training and this included training in abbreviated injury scale coding of injuries on CT brain scans by the Trauma Audit and Research Network (TARN) which is an Association for the Advancement of Automotive Medicine accredited trainer. A standardised electronic proforma (Appendix 37) was used by all researchers and data extraction including use of the proforma was piloted and refined over a 1-month period in 2 centres (Salford and Hull). Hypothetical and non-identifiable training samples of potential patient records were used for training all researchers completing data extraction and were used to check the quality of data-extraction

Weaknesses

The systematic review component of predictive model development was limited by the quality of studies identified. Most studies were small, retrospective and assessed outcomes over short time periods. Multiple definitions of clinical deterioration were used and these outcome measures were not intended by the authors to reflect need for hospital admission. Several studies selected patients on study specific characteristics for different care pathways or excluded higher risk patients from analysis. No studies were identified which were conducted in UK populations. These factors all contributed to an underestimation of the likely prevalence of deterioration in the conducted retrospective cohort study and consequent overestimation of the required sample size. Meta-regression assessing the effect of age on neurosurgical intervention in the review

presented in Chapter 4 found a cohort with an average age of 60 would have a prevalence of neurosurgical intervention of approaching 10% and prevalence of death around 4%. The conducted cohort study had a mean age of 58 years and a prevalence of neurosurgical intervention, ICU admission or intubation of 13.1% (95% CI: 11.6% to 14.8%) and death of 4.2% (95% CI: 3.4% to 5.3%). The younger average age of the participants in the majority of studies included in the review, compared to the cohort study may have further contributed to lower pooled prevalence of deterioration found in the conducted meta-analysis. Analysis of studies which included all GCS13-15 patients with injuries on CT imaging or European studies may have allowed a better estimate of the likely deterioration rate in the cohort study.

A prospective study design is the gold standard approach to developing a prognostic model.[78] As outlined in international prognostic research guidelines, a prospective design allows all relevant candidate factors and outcomes to be collected and measured using the best method, thereby reducing the chances of missing or poor quality data.[78] Prospective data collection also ensures findings are directly generalisable to current clinical populations and study estimates are not potentially affected by historical changes in management. However, due to the size of the cohort required, this was not feasible within the time and resource constraints of the supporting doctoral fellowship. The retrospective nature of the cohort study meant that the prognostic factors assessed were limited to those that were routinely collected and information regarding these factors was also limited by how they were recorded. This means the derived models used information currently available in clinical practice but that candidate factors identified in the review which were not routinely collected on most patients, such as venous lactate and blood glucose, could not be included. Additionally, novel prognostic factors such as biomarkers could not be assessed.[258]

Information available regarding type and severity of TBI was limited to that contained in written CT reports. These reports were not standardised and did not always include information on size of haemorrhage and presence of mass effect necessary to allow severity of injury to be accurately classified. Ideally, if time and resources had allowed,

the CT images would have been re-analysed to provide standardised information for the purposes of this study. Automated CT analysis may make this easier in the future.

Frailty was assessed using the Rockwood clinical frailty scale and a score was assigned using information present in the case notes in patients aged over 50.[221] The Rockwood frailty scale is intended to be applied in a face-to-face assessment but the retrospective nature of the study design prevented this. There is limited evidence that information in patient records can be used to accurately estimate a Rockwood Frailty Scale score in a community setting.[259] A prospective sub-study assessing whether a Rockwood Frailty Scale score can be accurately assigned using information recorded in NHS hospital records is currently being completed with collaborators at Bradford Royal Infirmary. This study was not planned as part of the fellowship or PhD and as frailty was not found to be predictive of the primary outcome measure of deterioration, this sub-study is not included in this thesis.

Around 25% of patients had missing data on one or more variables (Table 6.1), but as these data were mainly missing through poor recording or missing notes, and therefore missing at random, imputation techniques are likely to be valid. Recognised techniques for multiple imputation of missing data were used and the number of imputations needed were calculated using the proportion of missing data in the retrospective cohort,[237] as recommended in international prognostic research guidelines.[78] Case record documentation inaccuracies may have introduced random error but are unlikely to have introduced systematic bias.

The research team was not blinded to outcomes but most prognostic variables collected were demographic and most other clinical factors were not subject to interpretation. Determining whether ICU admission, death or readmission was due to TBI relied on the research team interpreting the information available in the case notes. Where reason for death, ICU admission or readmission was unknown it was attributed to TBI. In 35.5% of deaths and 12.5% of readmissions is was unknown whether the outcome was caused by TBI and therefore the prevalence of these outcomes may be overestimated.

Outcomes not recorded in hospital records such as deaths in the community or readmissions to other hospitals may have been missed. Local trauma registry submission numbers were used to check whether any deaths in the community were missed in patients in Hull eligible for entry onto the national trauma registry (TARN) database without research team members accessing patient identifiable data beyond the scope of their clinical practice. As the TARN registry is linked to ONS mortality data this allows any deaths in community not recorded in hospital records to be checked. No additional deaths were identified. CAG approval for research team to access patient identifiable information for community outcomes recorded in GP records could have been applied for. This may have introduced significant delays in completing the study and would have involved allowing access to more patient identifiable information without consent.

It was assumed that when no deterioration occurred this happened irrespective of presence or duration of hospital admission. It is possible that hospital admission may have prevented deterioration, even in the absence of specific treatment, through general patient care. This could include reversal of anti-coagulation, changes to medication including withholding anti-platelets and nursing care. Therefore, the model performance may in practice be worse than that estimated in this study, in which all patients were routinely admitted to hospital. This is a problem that would not be resolved by using a prospective cohort study. However, hospital admission generally is associated with risk of harm, especially in older patients, where it can precipitate acute confusion.[260] Therefore, the estimated prevalence of some of the components of the composite outcome of deterioration may be higher than if patients were not admitted. Ultimately, the most robust way to assess the impact and net effect of using the predictive model to discharge patients would be in a randomised trial.

As discussed in chapter 6, only internal validation of the derived prognostic models has been performed and therefore the estimated model performance may be optimistic. To adjust for optimism, bootstrap internal validation was performed using recognised statistical techniques and in accordance with prognostic research method guidance.[78, 236] There is debate about the best way to combine multiple imputation methods with bootstrap internal validation techniques.[244] As discussed in Chapter 6, a pragmatic

statistical approach to combining these two techniques was used, but this may underestimate the optimism of the developed prognostic model. As outlined in Chapter 5 it was hoped that data from an Italian cohort study[79] could be included to improve generalisability of study estimates through pooling. Unfortunately, factors including anti-platelet use, components of the neurological examination and Hb selected into the final models were not collected in the Italian cohort study, so preventing this.

Data were collected from 2010-2017, which is a significant period of time over which clinical management and the effectiveness of treatments may have changed. Notably, in 2014 the NICE head injury guidelines were updated and the indication for CT imaging in minor head injury changed for patients with pre-injury anti-coagulant use. Therefore, the performance of the model may vary over the time period. However, a sensitivity analysis comparing performance of the derived risk score before and after the introduction of the 2014 NICE guideline found no statistically significant difference in the sensitivity and specificity of the decision rule between the two periods (Appendix 38). Data were collected only at major trauma centres and therefore may reflect a more severely injured population due to pre-hospital emergency service selection of patients for care in specialist centres. Therefore, the results may not be generalisable to a peripheral trauma unit (district general hospital) TBI population.

Comparison to previous literature

The systematic review presented in chapter 4 is the first to assess the prevalence of, and risk factors for, deterioration in mTBI patients with injuries identified on CT imaging. No empirically derived prognostic models or risk stratification tools which could be used to identify low risk patients who could be discharged from the ED were found. A wide variation in admission practices were identified for this group internationally and especially in the USA, with a range of specialist admission and ED discharge criteria used in individual centres on the basis of limited evidence.[30, 31, 157, 178] The BIG criteria was identified as the only risk stratification tool in this population used to select low risk patients for discharge from the ED without further CT imaging and therefore applicable to UK practice where patients do not undergo routine repeat CT imaging.[80]

No studies conducted in a UK population were identified in review presented in Chapter 4. The research presented in chapter 6 therefore appears to report the first estimate of clinically important deterioration in this TBI population in the UK and the first empirically derived prognostic model which could be used to select patients for discharge from the ED.

As discussed earlier, the prevalence of deterioration estimated in the presented cohort was higher than the pooled average found in the systematic review (11.7%). The higher prevalence (27.7%) probably reflects differences in study population age, population selection and outcome measures. However, where cause of death, ICU admission or re-admission was unknown, it was attributed to TBI and included in the outcome measure. This may have additionally contributed to the comparatively higher estimated prevalence. The systematic review identified studies mostly completed in the USA. The reported retrospective cohort study is the first to estimate the prevalence of deterioration in this population in the UK. The study population was on average older with a lower GCS than those included in the review. Studies identified in the review had significant selection biases, limiting study populations to lower risk patients with: isolated injuries, higher GCS scores, with no pre-injury anti-coagulant or anti-platelet use. All GCS13-15 patients with injuries identified on CT imaging were included in the completed cohort study and a much wider composite definition of clinically important deterioration was assessed.

Two prognostic models were derived: the first predicting a wide primary composite outcome of deterioration encompassing need for hospital admission and a second predicting neurosurgery, ICU admission or intubation (need for specialist neurosurgical admission). The prognostic factors found to be most predictive in the meta-analysis reported in Chapter 4 and selected for in multivariable modelling were generally similar to those found in multivariable models for patients with more severe TBI.[86-88] In the completed systematic review, age, initial GCS, CT injury findings and pre-injury antiplatelet/anticoagulant use were found strong predictors of deterioration. Additionally, in the multivariable modelling, haemoglobin value, abnormal neurological examination and extra-cranial injury were found to be predictive of deterioration. No studies identified by the review evaluated the effect of an abnormal neurological exam on

deterioration. Only three studies assessed the effect of haemoglobin in the review and sometimes as a dichotomised variable.[27, 145, 170] Extra-cranial injury was not consistently reported in studies identified in the review and many studies excluded patients with extra-cranial injuries. This prevented pooling of the effect of these factors in the meta-analysis and may account for why they were found to be predictive of deterioration in the cohort study but not in the completed review.

GCS, extra-cranial injury, CT injury severity, brainstem injury, features of the neurological examination and Hb level have all previously been identified as prognostic factors in more severely injured patients than in the cohort reported in this thesis. [86-88] Within lower GCS TBI population, extra-cranial injury has also specifically been identified as a more important prognostic factor as GCS increases in individual patient data meta-analysis.[261] Pre-injury anti-coagulant and anti-platelet use were not considered for inclusion in these predictive models in a more severely injured TBI population. A laboratory measure of anti-coagulation was found to be predictive of worse clinical outcomes in the IMPACT study.[262]

Increasing age has consistently been found to be predictive of worse clinical outcomes in previous prognostic models for TBI.[86-88] Age was also found to be a strong predictor of deterioration in the systematic review reported in Chapter 4 but was not found to be predictive of the primary outcome of deterioration in the reported cohort study. Increasing age and frailty reduced the risk of invasive neurosurgical or ICU intervention in the reported cohort – but this may reflect a culture of reluctance to intervene surgically in older patients in this cohort rather than true clinical need. This contrast with previous TBI prognostic models probably reflects the differences in outcomes being assessed and modelling of clinical decision making. Previous models predicted survival to discharge and disability outcomes at 6 months.[86-88] A composite measures of deterioration up to 30 days from ED attendance was assessed which included selection for higher dependency levels of care or neurosurgery. Older patients may be less likely to be selected for invasive interventions due to greater frailty.

This thesis also presents the first independent assessment of the BIG criteria (Appendix 29). The team that developed this stratification tool in the USA assessed its performance in a Level 3 trauma centre in conjunction with another clinical team.[263] Around a third of patients in that study were categorised as BIG 1 and no adverse outcomes were reported in these patients. The BIG criteria performed less well in the reported study cohort and this may reflect differences in study population characteristics. The study population reported in Chapter 6 included a much higher proportion of patients with pre-injury anticoagulant and anti-platelet use, with a lower average GCS and older average age (Table 7.2).

Table 7.2: Thesis cohort versus BIG derivation cohort

Candidate Factor	**Category**	**Study Cohort Mean (SD), min-max OR N (%)**	**BIG Cohort Mean (SD), min-max OR N (%)**
Age	Years	58.2 (SD 23.3) 16-101	43.4
GCS	15 14 13	58% 31% 11%	Mean reported as 15
Preinjury Anti-coagulation or anti-platelets	Anticoagulation use Antiplatelet use Both	9% 17.3% 0.5%	2.5% 13.6%

Prognostic research in mTBI has focused on the wider population of all GCS13-15 patients who have evidence of functional or neurological impairment, including amnesia or disorientation, following head trauma.[212, 264, 265] In the absence of CT findings, these patients are not routinely admitted to hospital in the UK or internationally, but are at risk of long term neuro-cognitive symptoms and deficits. Although the reported systematic review and cohort study assessed short term outcomes in the subset of mTBI patients with CT findings, some recommendations for the conduct of prognostic research in mTBI made by the International Collaboration on mTBI prognosis are relevant to the reported cohort study.[265] The collaboration has identified, as in the reported review, small study sample size and population selection bias as common methodological weakness in mTBI prognostic research. As the cohort study presented in Chapter 6 was based on retrospective case note review, it was less susceptible to population selection biases that have been observed to occur in the prospective recruitment of mTBI patients. The

reported cohort study had a large sample size and was adequately powered to assess all the assessed prognostic factors.

The collaboration has also highlighted the lack of validated and universally applied outcome measures in mTBI research, particularly to measure long term neurocognitive diability.[265] A composite measure of deterioration aimed at encompassing need for hospital admission was used. As longer term neuro-psychiatric outcomes are not routinely assessed, even in CT positive mTBI patients, these could not be assessed in the cohort study reported in Chapter 6. A prospective cohort study of GCS13 and 14 mTBI patients found neurocognitive outcomes at 6 months to be unaffected by hospital admission or identification of injuries on CT imaging.[266] As the cohort study presented in Chapter 6 only contained patients with injuries identified on CT imaging, it may not be the best population in which to assess neurocognitive outcomes.

Interpretation

It was possible to derive a prognostic model and decision rule with a high enough sensitivity that it may be applied clinically. However, the low accompanying specificity means only a small proportion of patients would be discharged if the model were applied and a discharged patient would still have approximately a 1/50 chance of deteriorating. Such a high sensitivity for the model was selected as research into acceptable risk thresholds for the ED discharge of patients with chest pain indicates that clinicians and patients are happy for discharge from the ED if there is about a 1/100 risk of a subsequent serious adverse event occurring.[267, 268]

The higher than expected prevalence of deterioration in the reported cohort study and poor specificity of the model probably reflects the older age of the cohort and wide composite outcome of deterioration used. The high median age of the cohort and difficulties distinguishing between deterioration due to TBI and other medical factors causing a fall in GCS, such as infection and pre-existing dementia, means that recorded deterioration may have occurred due to factors unrelated to TBI and not considered for inclusion in the model. The factors identified for consideration for inclusion in the model

in the completed systematic review were primarily identified in a younger USA based trauma population. As older patients with extensive TBI are more likely to present with a high level of consciousness (GCS13-15),[165] the older age of the cohort in chapter 6 means a higher proportion of patients are likely to have extensive injuries than in cohorts previously assessing the BIG criteria.[31] This may account for the small proportion of patients in the reported cohort who were recommended for discharge by either the derived decision rule or the BIG criteria.

Overview and Implications

Overview

Head injury guidelines introduced in Scotland and England were intended to improve clinical outcomes through earlier detection of serious TBI, through increased CT imaging, and better management of patients with such injuries in specialist centres. Increased CT imaging was also meant to reduce health service costs by facilitating a reduction in head injury admissions. The analysis of Scottish and English administrative data found that the SIGN and NICE head injury guidelines appear to have been successful in achieving these aims in the 16-64 age group. At the time the second NICE guideline was introduced in 2007 there were around 0.7 inpatient deaths and 40 admissions attributable to TBI per 100, 000 population. By the end of the end of study period in 2017, this had fallen to around 0.4 deaths and 20 admissions per 100 000 population. In 2017 there were estimated to be 34,963,654 people aged between 16-64 in England (NOMIS mid-year population estimate) equating to around 105 lives saved and 6992 TBI admissions avoided that year.

The large increase both in admissions and deaths attributable to TBI observed in older patients is largely unexplained and requires further investigation. In absolute terms, inpatient deaths and admissions attributable to TBI in England increased from 453 and 10,553 in 1999, to 2,155 and 35,488 in 2016 (the population of England aged 65+ increased by 27% over this period). As previously predicted, increased CT imaging of minor head injured patients was found to be associated with an increase in admissions

for patients with injuries identified radiologically who did not require intervention.[18] In Scotland from 2010-2016 around 650 extra admissions, across the whole period, could be attributed to increased CT imaging associated with the introduction of the second SIGN guideline (Appendix 8: calculated using an average of yearly population estimates).

Current guidelines could be made more cost effective by reducing the proportion of patients with TBI identified by CT imaging (but are at a low risk of deterioration) who are admitted. All patients with injuries identified by CT imaging are routinely admitted to hospital but the majority of such patients with an initial GCS13-15 do not deteriorate, or require any specific intervention, and so admission appears to be largely unnecessary. If patients who aren't going to deteriorate can be accurately identified and safely discharged from the ED, then this would benefit patients and save health service resources. As the resolution of CT imaging continues to improve, due to increases in the number of slices measured and reduction in slice thickness, it is likely that more injuries will be identified radiologically.[269] This combined with calls to adopt international guidelines which advocate further increases in CT imaging of minor head injured patients is likely to lead to further increases in admissions for patients with TBI identified radiologically.[74]

The good performance of the prognostic model and risk score derived in this thesis shows it is likely to be possible to identify low risk patients with injuries identified by CT imaging who can be safely discharged from the ED. In the cohort study reported in Chapter 6, application of the derived decision would have resulted in the discharge of 5.5% of those patients currently routinely admitted to hospital. As GCS score does not form part of coding in NHS administrative data sets it is difficult to accurately estimate the potential impact of application of the model nationally. However, using HES data, it was estimated that there were 74,242 admissions for TBI in England in 2016 and 95% of head injured patients attend with an initial GCS13-15.[269] In cohort presented in Chapter 6, 372 patients were identified for inclusion in 2017 at three English Major Trauma Centres. There are 22 Major Trauma Centres for adults in England and 168 acute trusts.[270, 271] Assuming a minimum of twice as many patients attend non-Major Trauma Centres, application of the decision rule would avoid around 500 hospital admissions a year.

Implications for policy and practice

The evidence presented in this thesis suggests that the implementation of current head injury guidelines has been less effective at reducing TBI deaths and hospital admissions in the 65+ age group. As previously discussed, apparent increases in TBI in this age group may reflect better case ascertainment of an existing disease burden through increased CT imaging. However, irrespective of cause of increased TBI mortality rate in older patients, specialist services may need to be expanded to improve outcomes in this group. The UK has one of the lowest numbers of Intensive Care Unit (ICU) beds per population in Europe. In 2012 it was estimated that the UK has less than 5 ICU beds per 100 000 population, compared with around 10 in France and 25 in Germany.[74] When the 2007 NICE guideline recommendation regarding management of patient in specialist centres was made, concerns were raised about the system meeting demand.[22] If management of severely injured patients in specialist centres is more effective than in non-specialist facilities in those aged 65+, and older patients have unequal access, then significant increases in access and service provision may be necessary to improve outcomes.

The introduction of the 4-hour target was associated with an increase in both head injury and TBI admissions, with no associated mortality benefit. This costly unintended increase in admissions reflects interaction between the 4-hour target and guideline recommendations for the timing of CT imaging. As has been previously argued, performance targets need to be carefully considered before implementation to ensure that they do not have unintended consequences, in this case undermining the benefits of evidence-based clinical guidelines.[62] A more granular approach to the 4-hour target may have helped prevent admissions to avoid breeches of the target where patients are solely awaiting investigations, such as CT imaging in head injury. Time to CT imaging in older patients recommended in current guidelines may need to be made shorter if the guidelines are to be cost effective, on the basis of a reduction of admissions, in the 65+ age group.

Current practice for mTBI patients with injuries identified by CT imaging in the UK is routine admission for observation of all patients. This practice is conservative and reflects

a lack of evidence and therefore uncertainty about which patients are at significant risk of deterioration. Centres in the USA use various criteria, including the BIG risk stratification tool, to select low risk patients for discharge from the ED.[31, 129] The BIG criteria has the most evidence to support its use but has not previously been assessed in a UK population. As all patients in this population are currently admitted for observation in the UK, clinical application of either the derived decision rule or the BIG criteria to reduce admissions could potentially save significant health service resources. Between April 2014 and June 2015 around 6000 patients mTBI with injuries on CT imaging were admitted to Major Trauma Centres in England.[8] Application of the derived decision rule, if study estimates are accurate, would had allowed around 5% of these patients to be discharged from the ED, so saving health care resources and reducing patient inconvenience and anxiety.

The decision to clinically implement prognostic models is not a simple undertaking and should be informed by research to demonstrate reproducibility of model performance and improved outcomes resulting from clinical use.[272] Any benefits from use of the decision rule must be considered alongside the costs of implementation and acceptability of its use. The higher than predicted prevalence of deterioration in the reported cohort meant that even with a 99.5% sensitivity to the primary outcome, a negative predictive value of 97.7% was achieved (about a 1 in 50 chance of a discharged patient deteriorating). Decision rules resulting from prognostic models must be acceptable to both clinicians and patients if they are to be applied. A 1 in 50 chance of a discharged patient deteriorating may be too high a risk for either group, even if (as in the study reported in Chapter 6) no patient recommended for discharge had the most severe outcomes of deterioration or required invasive intervention. The attitude to risk of clinicians and patients would need to be explored to determine whether the discharge criteria would be likely to be implemented.

For older frail patients with advanced disease processes or who are from residential of nursing homes, the broad primary outcome measure of deterioration used to encompass need for hospital admission may not be appropriate. Discharge to a supervised environment means the risks associated with a drop in GCS or seizure are likely to be smaller whilst the potential harm associated with hospital admission, such as functional

decline, is greater.[273] Assessment of performance of the model in predicting a more relevant outcome of deterioration for older fail patients with lower energy mechanisms of injury is required.

A range of barriers has been identified that prevent implementation of prognostic models in clinical practice, even when clinicians support their use.[274] These barriers would have to be overcome if the model were to be widely used in clinical practice. Without external validation and further implementation research UK clinicians are rightly unlikely to adopt the derived decision rule over current more cautious practice of routine admission for observation.

Implications for research

As individual level data were not available for Scotland, it was not possible to replicate identical analysis in the English and Scottish data sets used for this research. Future research using individual level Scottish administrative data to evaluate the impact of the SIGN guidelines on TBI mortality could provide further evidence as to which head injury guidelines are clinically effective and in which age group. The confounding effect of the 4-hour target makes interpreting the impact of NICE guidelines on admissions for head injury in England more challenging. However, further research is planned to assess whether the observed increase in admissions for patients with TBI identified radiologically, possibly of lower severity, associated with the introduction of SIGN guidelines also occurred in England when the NICE guidelines were introduced.

Much head injury research has focused on deriving decision rules to determine which patients with minor head injury require CT imaging.[74] Identification of injuries alone may be necessary, but without access to appropriate specialist care, does not appear sufficient to improve outcomes. Patel et al were unable to identify what aspect of specialist care reduced mortality in severely injured patients, but suggested it was likely to be multi-factorial.[21] Fuller et al have hypothesised that the mortality benefit observed in severely injured patients associated with increased management in specialist centres may result from the development of neuro-critical care as a clinical subspecialty, stricter adherence

to international clinical guidelines, increasing levels of intra-cranial pressure and multi-modality brain monitoring.[23]

Specialist stroke units have been found to reduce mortality in stroke patients but despite extensive research the mechanism remains debated and is regarded as a "black box".[275-278] How specialist care reduces mortality in severely injured TBI patients, even in the absence of operative management, is likely to be similarly complex and difficult to unpack. NHS administrative data sets and TARN data are unlikely to contain the depth of information necessary to disentangle which components of specialist care are resulting in the observed benefit. However, given the limited availability of specialist care, better understanding of the mechanism of effect could be useful in identifying who is most likely to benefit and whether mortality reductions are replicable in non-specialist environments.[22] This may require different research methods to previous studies analysing TARN data which demonstrated mortality benefits and may need to be aimed at evaluating complex multifactorial interventions.[279]

In planning the NIHR Doctoral fellowship application which funded the research for this thesis, a range of patient groups were consulted including the Hull branch of Headway, a charity which provides support for people living with the effects of acquired brain injury. They highlighted that an area of unmet need resulting from improved TBI care was an increase in patients surviving with significant disabilities. As one participant said: "you save our lives and then leave us with nothing". This group felt that emergency hospital care was generally good. However, the unintended outcome of this was that more patients survived with disability needs that were not being met. Current TBI research is limited by the availability of good quality routinely collected data, with use of ICD coding to classify severity of injury and poor collection of disability outcomes highlighted as particular problems.[3] Assessing how the prevalence of TBI associated disability has changed following the introduction of clinical head injury guidelines represents an important area for future research but not was possible as part of this fellowship as disability outcomes are not routinely collected in NHS administrative data sets. Improved data collection in TBI, as advocated by the Lancet Neurology Commission, may be necessary to allow such further research to occur.[3]

The large increase in TBI deaths observed in those 65+ in England is of concern. This occurred despite increasing hospital admissions for TBI and head injury across the study period in both England and Scotland, indicating that clinical management may be less effective in this age group. The cause of the increase in TBI mortality rate in those 65+ and the identification of effective clinical interventions requires further research. Analysis of TARN data has found large increases in the number and proportion of older TBI patients, disproportionate to changes to population demographics, in the period following the introduction of the NICE head injury guidelines.[56] The 65+ age group contains the largest number of NICE guideline indications for CT imaging following head trauma and it has been argued that apparent increases in TBI in this age group may reflect better case ascertainment due to increased diagnostic precision from CT imaging. Others have linked large increases in TBI in older patients observed across Europe to falls, comorbidities, increasing frailty and changing life-style factors.[3]

Better understanding of the cause of increases in TBI in older people is required if public health interventions are to be appropriately targeted. The Lancet neurology commission has highlighted the association between frailty in the elderly and falls which result in TBI as a potential modifiable risk factor for TBI in this age group.[3] The commission proposed the use of community frailty assessments and targeted falls prevention services as possible effective interventions which need further evaluation. The commission also highlighted that a lack of standardised routine data collection mechanisms to monitor TBI incidence, prevalence and outcomes has prevented high quality population based epidemiology studies. Therefore, improved routine data collection may be necessary to identify other potential targets for primary prevention of TBI in older patients.

Even if observed increases in TBI in the 65+ age group result from better case ascertainment, the high prevalence still represents a major health service challenge which requires effective interventions. In the reported cohort study, increasing age and frailty were found to reduce the likelihood of operative and ICU intervention. This supports findings from TARN data which found older trauma patients to be less likely to receive treatment in specialist centres and experience delays in and reduced likelihood of interventional management even when admitted to specialist centres.[56] Older frail

patients may be less likely to benefit from invasive and operative intervention and so this may be entirely appropriate. Increasing age in those over 65+ irrespective of type of intervention has been found to increase likelihood of death following TBI, and frailty is an independent predictor of adverse outcomes.[234, 280] There is evidence that in subdural haemorrhage, more common in the elderly, careful selection of patients for operative and specialist management after a period of observation leads to better outcomes.[70]

Others have argued that poor outcomes in older TBI patients may be a self-fulfilling prophecy as older patients are not selected for potentially life-saving treatments as they are expected to have poor outcomes.[281] Research is needed to help identify which older TBI patients may benefit from operative and specialist management and alternative effective care pathways for other older patients.

Using Scottish data, evidence was found to indicate that increased CT imaging associated with the implementation of national head guidelines is associated with an increase in radiologically identified TBI which does not require neurosurgery. The prognostic model developed in the second part of this thesis is specifically aimed at reducing hospital admissions in those patients with TBI identified radiologically who do not require clinical interventions. Application of the derived model may eventually help reverse large increase in TBI admissions observed in older patients. The prognostic model was developed on data for all age groups and application specifically to those 65+ would require recalibration of the model with coefficients re-estimated to optimise performance for this group. However, 44.5% of patients in the reported cohort were aged 65+ and only one of the two patients who deteriorated and would have been selected for discharge was aged over 64. This indicates the derived model may perform as well for an older population as for the whole cohort, but this needs to be specifically assessed.

The risk score derived from the prognostic model achieved a 99.5% sensitivity to the primary composite outcome of deterioration and outperformed the BIG criteria in terms of specificity. However, application of the discharge decision rule to the reported cohort would only have resulted in the discharge of 5.5% of patients currently admitted, due to the low specificity at that level of sensitivity. Future research which includes standardised

reporting of CT images to include size and other makers of severity of injury may improve the performance of the model. The prognostic value of novel and non-routinely collected candidate factors such as venous lactate and bio-markers also requires assessment and inclusion may allow the discharge of more patients without a loss of sensitivity.[27, 258]

Given the tendency of derived models to perform optimistically in data sets in which they are derived and the limitations of the retrospective study design used to develop the prognostic model, prospective validation is required before the model estimates can be regarded as accurate within the context of current admission practices.

Even if the estimated performance of the model found in this derivation cohort is reproducible in a range of equivalent populations, additional research is required for effective implementation.[78] This includes implementation and impact studies to assess whether the model is acceptable to clinicians and patients and assess whether use of the model improves clinical care.[272] Application of the derived model would involve discharging patients from the ED with a small risk of subsequent deterioration and evaluating the acceptability, benefits and costs of this would be the final step, following external validation, before potentially recommending routine use.

The research presented in this thesis has found evidence that an unintended consequence of increased CT imaging of minor head injured patients has been an increase in hospital admissions for patients with injuries identified by CT imaging who do not require neurosurgical intervention and who may have lower severity injuries. The research then focused on ways to reduce hospital admissions for such patients through improved prediction of adverse outcomes. However, the methods used by research aimed at determining which minor head injured patients require CT imaging could be improved in order to reduce the number of non-clinically significant injuries which are identified. The Canadian CT Head Rule derivation study measured neurosurgery or death as its primary outcome for determining which patients required CT imaging.[9] However, in more recent research, the goal of derived decisions rules has been to ensure that no radiologically identified injuries are missed. [74] As CT imaging performance continues to improve, the use of any radiologically identified injury as a primary outcome in such

research may mean that studies are assessing an ever-more frequent but less clinically important end point, resulting in further increases in admissions for patients who do not benefit. Future research, using clinically important outcomes, could improve the specificity of current decision rules, reducing CT imaging and the radiological identification of non-clinically significant injuries.

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Appendices

Appendix 1: The Sign Head Injury Guidelines and 4 hour target

Policy	**Time of Introduction**	**Key Features**
1st SIGN Head Injury Guideline	August 2000	Indication for CT imaging (referenced directly from 2000 SIGN guideline): (1) GCS<13 (2) A deteriorating level of consciousness or progressive focal neurological signs (3) Confusion or drowsiness (CGS 13 or 14/15) followed by failure to improve within at most four hours of clinical observation (4) Radiological/clinical evidence of a fracture, whatever the level of consciousness (5) New focal neurological signs which are not getting worse (6) Full consciousness (GCS 15/15) with no fracture but other features, including: – severe and persistent headache – nausea and vomiting – irritability or altered behaviour – a seizure. Skull films should be carried out if any of the following apply and if CT is not being performed: If the patient is alert and orientated and obeying commands (GCS 15/15) but: – the mechanism of injury has not been trivial; or – consciousness has been lost; or – the patient has loss of memory or has vomited; or – the scalp has a full thickness laceration or a boggy haematoma; or – the history is inadequate.
4-Hour ED performance target	2004	98% of patients attending the ED to be assessed, treated and either discharged or admitted to hospital within 4 hours of arrival. Financial incentives associated with meeting the target.
2nd Sign Head Injury Guideline	May 2009	Referenced directly from 2nd SIGN Guidelines Indications Immediate CT scanning (adult): - GCS<13/15 - GCS 13/15 or 14/15 followed by failure to improve within one hour of clinical observation - base of skull or depressed skull fracture and/or suspected penetrating injuries - a deteriorating level of consciousness or new focal neurological signs - GCS 15/15 with severe and persistent headache or two episodes of vomiting - coagulopathy (eg warfarin use) and loss of consciousness or amnesia Indications CT scanning within eight (adult): - age>65 (with loss of consciousness or amnesia) - clinical evidence of a skull fracture but no clinical features indicative of an immediate CT scan - any seizure activity

		- significant retrograde amnesia (>30 minutes) - dangerous mechanism of injury Indications Immediate CT scanning (<16 years): - GCS≤13 on assessment in ED - witnessed loss of consciousness >5 minutes - suspicion of open or depressed skull injury or tense fontanelle - focal neurological deficit - any sign of basal skull fracture. Indications CT scanning within 8 hours (<16 years): - presence of any bruise/swelling/laceration >5 cm on the head - post-traumatic seizure - amnesia (anterograde or retrograde) lasting >5 minutes - clinical suspicion of non-accidental head injury - a significant fall - age under one year: GCS<15 in emergency department - three or more discrete episodes of vomiting - abnormal drowsiness.

Appendix 2: The features of the NICE head injury Guidelines

Policy	Introduced	Key Features
1st NICE Head Injury Guideline	June 2003	Indication for CT imaging (referenced directly from 2003 Guideline): - GCS <13 at any point from injury. - GCS equal to 13 or 14 at 2 hours after the injury on assessment in the emergency department. - Suspected open or depressed skull fracture. - Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid otorrhoea, Battle's sign). - Post-traumatic seizure. - Focal neurological deficit. - More than one episode of vomiting. - Amnesia for greater than 30 minutes of events before impact. CT should also recommended in patients with any of the following risk factors, provided they have experienced some loss of consciousness or amnesia since the injury: -Age greater than or equal to 65 years. -Coagulopathy (history of bleeding, clotting disorder, current treatment with warfarin). -Dangerous mechanism of injury (a pedestrian struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or five stairs).
2nd NICE Head Injury Guideline	September 2007	Specialist management (referenced directly from 2007 Guideline): Local guidelines on the transfer of patients with head injuries should be drawn up between the referring hospital trusts, the neuroscience unit and the local ambulance service, and should recognise that: -Transfer would benefit all patients with serious head injuries (GCS<9), irrespective of the need for neurosurgery -If transfer of those who do not require neurosurgery is not possible, ongoing liaison with the neuroscience unit over clinical management is essential. Indications Immediate CT scanning (adult): - Glasgow coma score <13 on initial assessment in the emergency department - Glasgow coma score <15 two hours after the injury on assessment in the emergency department - Suspected open or depressed skull fracture - Any sign of basal skull fracture - Post-traumatic seizure - Focal neurological deficit - One or more episodes of vomiting - Amnesia for events more than 30 minutes before impact. Indications Immediate CT scanning (<16 years): - Age over 1 year: Glasgow coma score <14 on assessment in the emergency department - Age under 1 year: Glasgow coma score paediatric <15 on assessment in the emergency department - Age under 1 year and presence of bruise, swelling, or laceration (>5 cm) on the head

		- Clinical suspicion of non-accidental injury - Post-traumatic seizure but no history of epilepsy - Abnormal drowsiness - Suspected open or depressed skull injury, or tense fontanelle - Any sign of basal skull fracture - Focal neurological deficit - Three or more discrete episodes of vomiting - Amnesia (antegrade or retrograde) lasting more than five minutes.
3rd NICE Head Injury Guideline	January 2014	Referenced directly from 3nd NICE Guidelines Indications CT scanning < 1 hour (adult): - GCS<13/15 - GCS <15 after2 hours from injury - Suspected open or depressed skull fracture - Any sign of basal skull fracture - Post-traumatic seizure - Focal neurological deficit - One or more episodes of vomiting Indications CT scanning < 8 hours (adult): - Patient taking warfarin - LOC or amnesia + dangerous mechanism/age 65+/history of bleeding/clotting disorder - Amnesia for events more than 30 minutes before impact. Indications CT scanning < 1 hour (<16 years) if 1 of: - Suspicion of non-accidental injury - Post-traumatic seizure but no history of epilepsy. - On initial emergency department assessment, GCS less than 14, or for children under 1 year GCS (paediatric) less than 15. - At 2 hours after the injury, GCS less than 15. - Suspected open or depressed skull fracture or tense fontanelle. - Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign). - Focal neurological deficit. - For children under 1 year, presence of bruise, swelling or laceration of more than 5 cm on the head. Indications CT scanning < 1 hour (<16 years) if 2 or more of: - Loss of consciousness lasting more than 5 minutes (witnessed). - Abnormal drowsiness. - Three or more discrete episodes of vomiting. - Dangerous mechanism of injury - Amnesia (antegrade or retrograde) lasting more than 5 minutes[4]. If only 1 above risk factor observe for 4 hours post injury if during observation develop any risk factor below for CT within 1 hour - GCS less than 15. - Further vomiting. - A further episode of abnormal drowsiness. If taking warfarin for CT within 8 hours.

Appendix 3: NIHR DRF application Scientific abstract (December 2015)

Background:

Every year there are 1.4 million attendances to Emergency Departments in England and Wales following a head injury. A small number of these patients have significant brain injuries and are at risk of death without neurosurgical intervention.

NICE guidelines were introduced in 2003 to improve outcomes following head trauma. They recommended increased use of computed tomography (CT) head imaging to detect significant brain injuries and the management of patients with severe injuries in specialist centres. The guidelines were expected to reduce deaths and hospital admissions. The impact of the NICE head injury guidelines on mortality and admissions has not been rigorously assessed. Almost all mild traumatic brain injury patients who have minor CT head scan abnormalities are admitted to hospital due to the risk of deterioration. However, only 15% of admitted patients deteriorate. Better understanding of the factors influencing patients' risk of deterioration will allow hospital admissions to be better targeted.

Aim:
This research will assess the impact of the NICE guidelines and how they can be refined to reduce unnecessary hospital admissions.

Objectives:
1) Assess the impact of the introduction of the NICE guidelines on deaths from traumatic brain injury.
2) Assess the impact of the introduction of the NICE guidelines on the number and rate of hospital admissions due to head injury.
3) Assess whether any increase in admissions are due to the identification of more traumatic brain injuries that do not require neurosurgery.
4) Develop a prognostic model that risk stratifies mild traumatic brain injury patients who have minor CT head scan abnormalities and estimate the extent to which hospital admissions could potentially be reduced by its use.

Plan of investigation:
Hospital episode statistic data linked to Office of National Statistics mortality data will be used to identify hospital admissions and deaths due to head injury from 1998 to 2016. An interrupted time series analysis will be conducted to assess the impact of the introduction of NICE head injury guidelines in 2003 (revised in 2007 and 2014) on level and trends in traumatic brain injury deaths and hospital admissions due to head injury.

Analysis of a subset of traumatic brain injury patients with diagnostic codes related to abnormalities detected by CT head imaging will be completed. The impact of the introduction of the NICE guidelines on the level and trends of hospital admissions and neurosurgery in this group will be assessed using an interrupted time series analysis.

To develop a clinical risk model, I will first conduct a systematic review, using international standards, to identify patient and radiological factors associated with poor outcomes in mild traumatic brain injury patients that have minor CT head scan abnormalities. I will then estimate how well these factors predict deterioration in a retrospective cohort of patients. Logistic regression will be used to estimate a prognostic model. The predictive accuracy of this will be assessed by applying it to another retrospective cohort of patients. The risk model will be used to develop a clinical-risk tool to inform discharge decisions. I will estimate the potential impact on admissions of using this model

Benefit to patients and the NHS:
Implementing the NICE head injury guidelines represented a large expenditure of NHS resources. It is important to assess whether these guidelines have been effective, and potentially caused an increase in unnecessary hospital admissions.

Developing a clinical risk assessment tool for mild traumatic brain injury patients that have minor CT head scan abnormalities will help refine the NICE head injury guidelines to allow better risk stratification of this group. Better risk stratification would inform shared decision-making and could reduce the rate and length of admissions.

Appendix 4: Data acquisition, governance and handling

The data extract used for the analysis presented in Chapter 2 was provided by Information Service Division Scotland in a pre-aggregated form with small numbers suppressed in line with National Health Service guidelines. The data provided were pre-aggregated on a monthly basis and there was no possibility for linkage to other data sets and for the potential identification of individual patients. Therefore, no specific data governance requirements were needed for the use of these data and the monthly aggregated outcomes were converted into monthly rates using mid-year population estimates and analysed directly. Ethically, these data are fully anonymised aggregated routinely collected secondary administrative data which are publicly available upon request and therefore no specific ethical approval was required for their use.

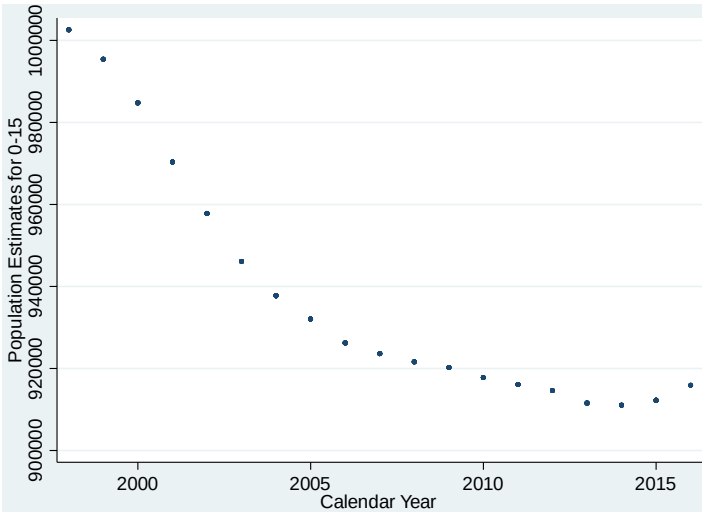
The data extract provided by NHS digital for the analysis presented in Chapter 3 was fully anonymised routinely collected health data but as they were provided at an individual level there was a theoretical risk an individual could be identified if the data provided was linked to other data sets. Therefore, a formal application was made to NHS digital for provision of the data extract and for its use in this specific project. This included an information governance and security assessment of both the University of York and University of Hull by NHS digital. As Health Sciences at the University of York had the required NHS Digital approved Information Governance Tool Kit in place, these data were stored on a secure and isolated SQL server there. As I was employed by the University of Hull it acted as the overall data controller and the University York acted as the data processor. Processing of the data in this way was subject to a formal data sharing agreement between NHS Digital and the University of Hull and a further data sharing agreement between the University of York and Hull. The use of theses individual level data for this project underwent internal data governance review by both the University of York and University of Hull before the data agreement was signed. Linkage of the data to other data sets was strictly prohibited. This ensured that individuals could not be identified from the data extract provided.

In accordance with the formal data agreement individual level data were only accessed by named members of the research team including myself and my supervisors employed by the University of York. Individual level data were only accessed and processed on a single isolated secure computer with access to the secure server containing the data extract. Individual level data were aggregated into monthly and yearly totals on the SQL server using the computer language SQL. These aggregates were transferred to STATA and converted into rates using mid-year population estimates for England. Monthly rates were then used for the interrupted time series analysis presented in Chapter 3. Small numbers were suppressed in accordance with NHS digital guidelines.

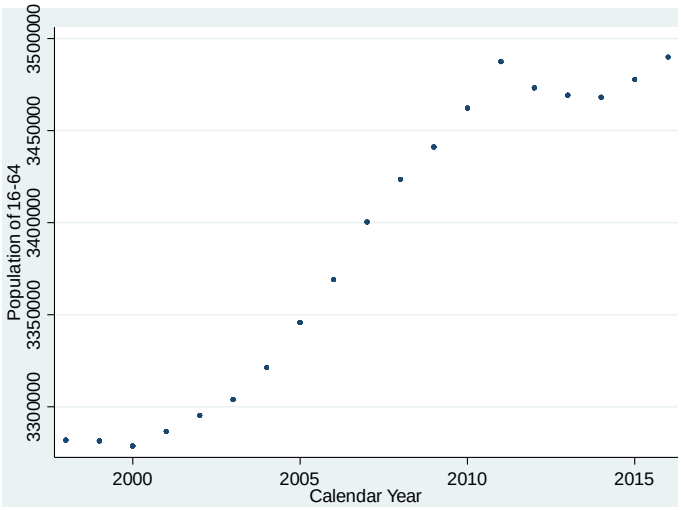
The data extract provided by NHS Digital is now in the process of being destroyed in accordance with NHS digital guidelines. Upon destruction the data sharing agreement will be terminated.

Appendix 5: Changes to Scotland's population structure

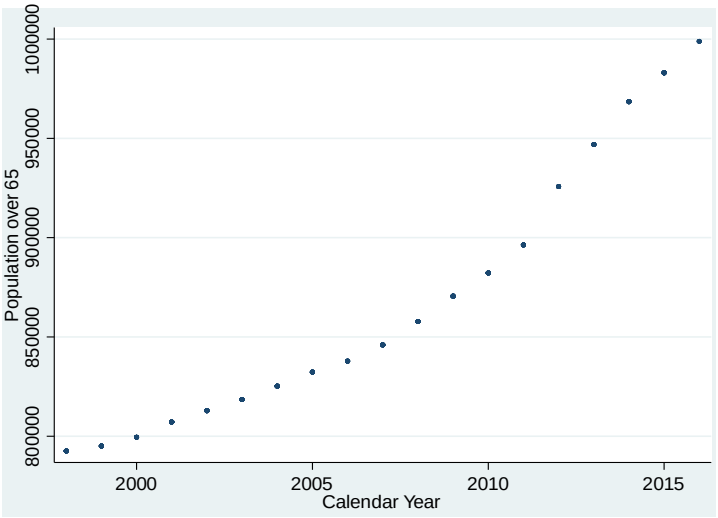
i) Mid-year Estimate Scottish Population 0-15



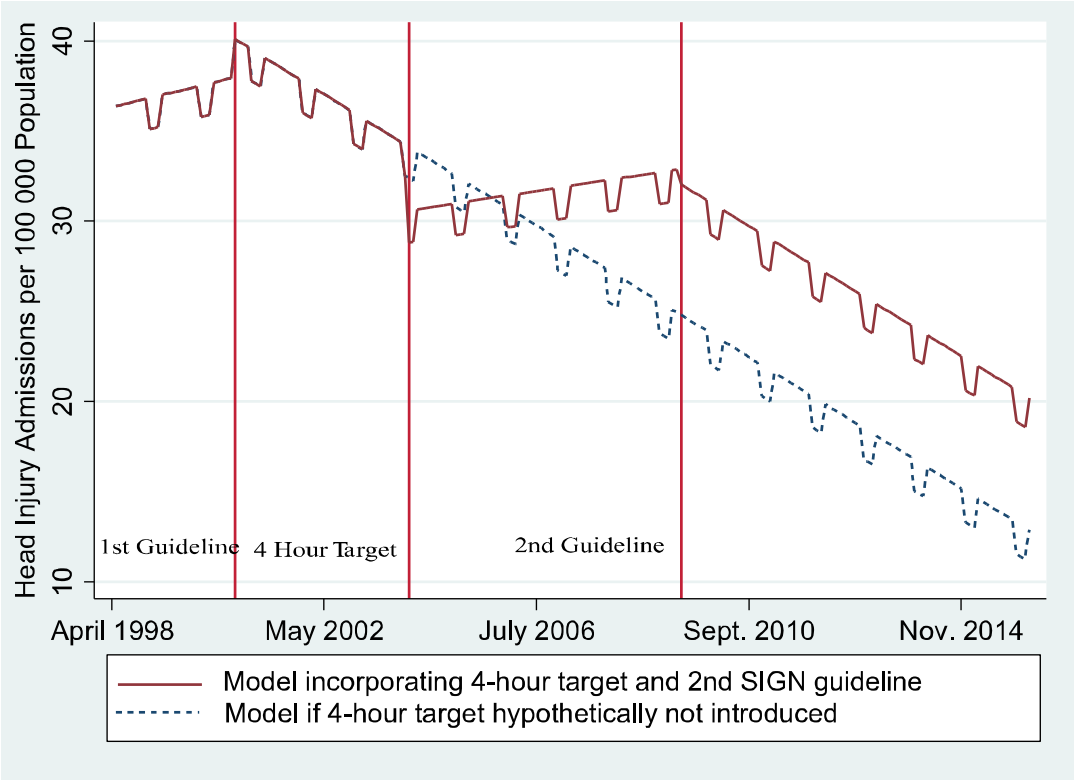
ii) Mid-year Estimate Scottish population 16-64



iii) Mid-year Estimate Scottish population 65+



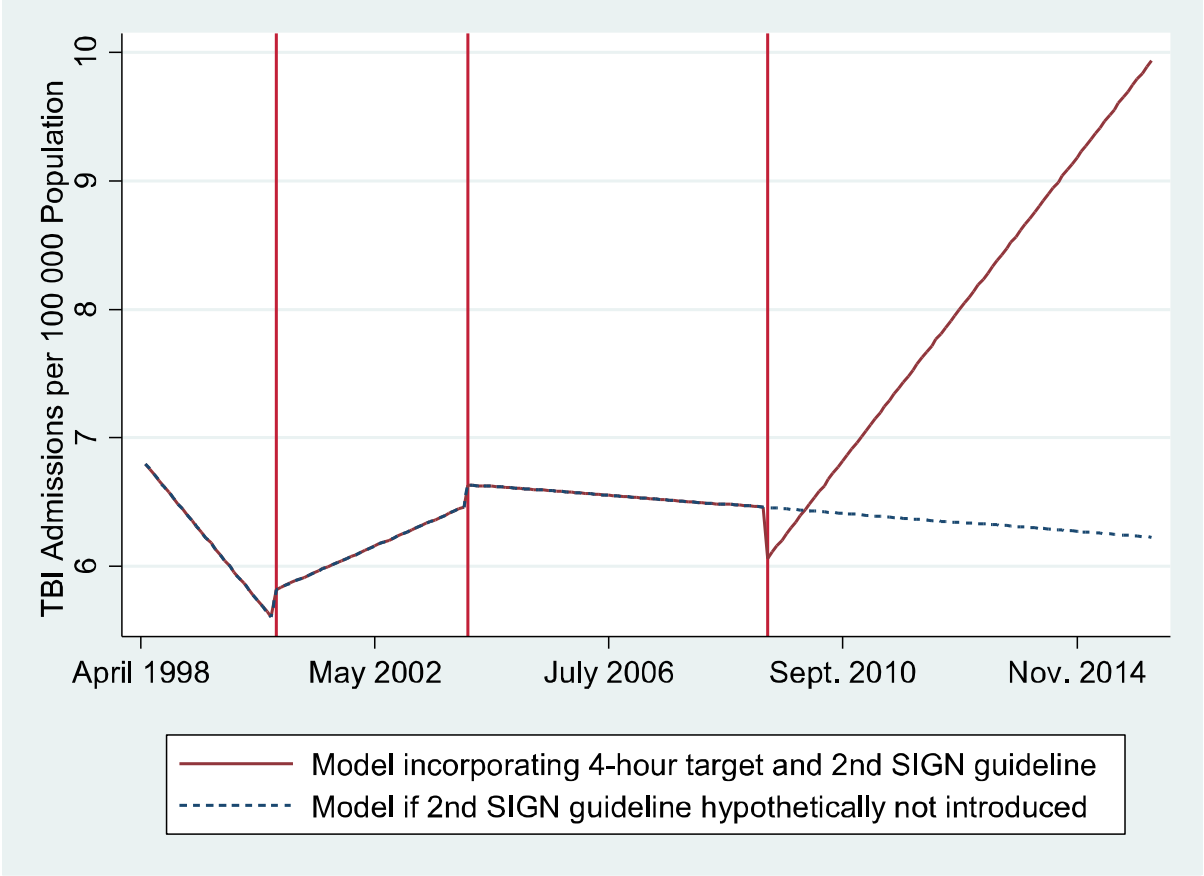
Appendix 6: Increase in admissions related to the introduction of the 4-hour target in the 16-64 age group



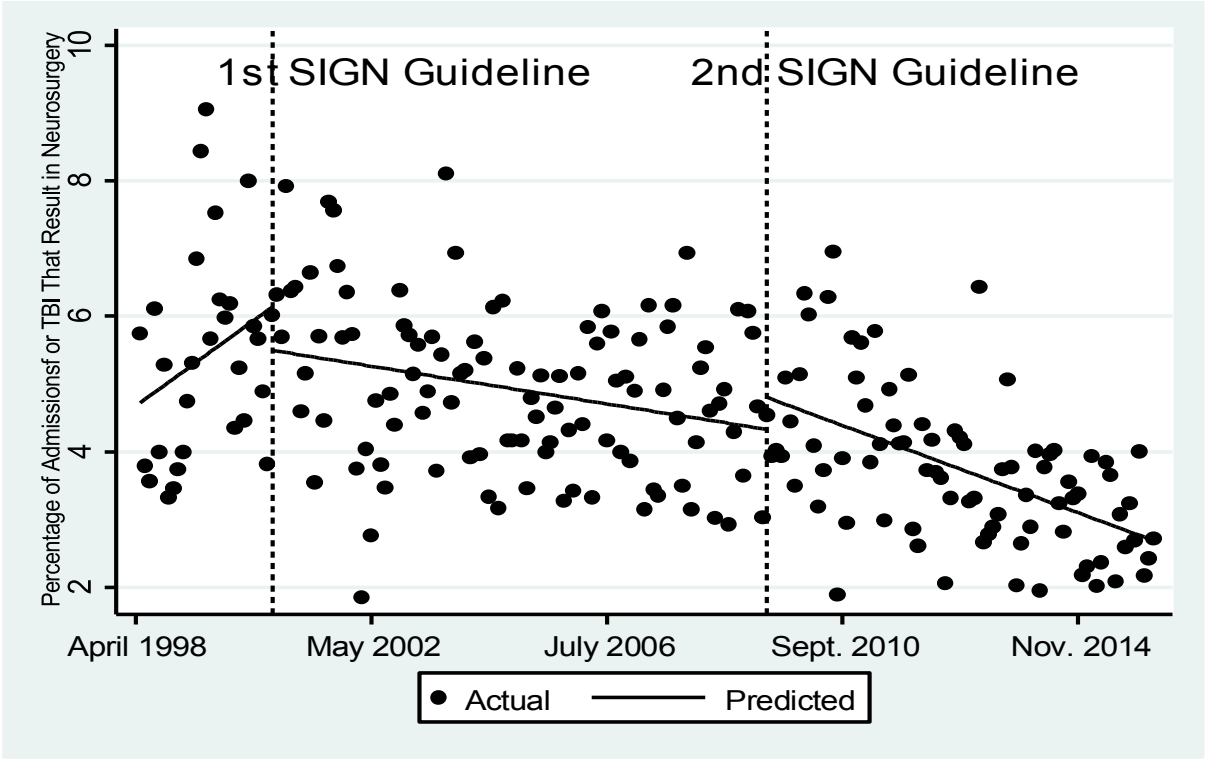
Appendix 7: Estimate of Impact of the SIGN guidelines and introduction of 4-Hour Target admissions for head injury with 12-month time lag

Age Band	Winter	Initial Trend	1st SIGN Guideline	4-hour Target Introduced	2nd SIGN Guideline	Durbin-Watson Statistic
All ages	-3.00 (95% CI: -3.75 to -2.26) P<0.01	0.04 (95% CI: -0.07 to 0.14) P=0.48	**Change level:** 2.66 (95% CI:0.27 to 5.04) P=0.03	**Change level:** -2.73 (95% CI:-4.85 to -0.61) P<0.01	**Change level:** -2.07 (95% CI:-3.74 to -0.40) P=0.02	Untransformed 1.77 Prais-Winsten 2.00
			Change trend: -0.23 (95% CI:-0.38 to -0.08) P<0.01	**Change trend:** 0.25 (95% CI: 0.14 to 0.36) P<0.01	**Change trend:** -0.13 (95% CI: -0.18 to -0.08) P<0.01	
0-15	-9.31 (95% CI: -11.05 to -7.59) P<0.01	-0.18 (95% CI:-4.89 to 0.13) P=0.26	**Change level:** 8.53 (95% CI:1.93 to 15.13) P=0.01	**Change level:** 1.61 (95% CI:-4.39 to 7.61) P=0.60	**Change level:** -1.71 (95% CI:-6.61 to 3.20) P=0.49	Untransformed 1.37 Prais-Winsten 1.85
			Change trend: -0.17 (95% CI:-0.61 to 0.28) P=0.47	**Change trend:** 0.15 (95% CI: -0.17 to 0.48) P=0.36	**Change trend:** 0.10 (95% CI:-0.50 to 0.26) P=0.18	
16-64	-1.80 (95% CI:-2.56 to -1.04) P<0.01	0.06 (95% CI:-0.06 to 0.17) P=0.34	**Change level:** 1.29 (95% CI:-1.28 to 3.85) P=0.32	**Change level:** -4.19 (95% CI:-6.48 to -1.89) P<0.01	**Change level:** -3.06 (95% CI:-4.88 to -1.24) P<0.01	Untransformed 1.57 Prais-Winsten 2.05
			Change trend: -0.25 (95% CI:-0.41 to -0.09) P<0.01	**Change trend:** 0.29 (95% CI: -0.17 to 0.40) P<0.01	**Change trend:** -0.25 (95% CI:-0.30 to -0.19) P<0.01	
65+	1.69 (95% CI: 0.22 to 3.17) P=0.03	0.17 (95% CI:-0.04 to 0.38) P= 0.10	**Change level:** 3.64 (95% CI:-1.08 to 8.36) P= 0.13	**Change level:** -1.64 (95% CI:-5.83 to 2.55) P=0.44	**Change level:** 2.30 (95% CI:-1.00 to 5.60) P=0.17	Untransformed 1.78 Prais-Winsten 2.00
			Change trend: -0.22 (95% CI:-0.51 to 0.07) P=0.14	**Change trend** 0.26 (95% CI: 0.04 to 0.48) P=0.02	**Change trend:** 0.003 (95% CI:-0.10 to 0.10) P=0.95	

Appendix 8: Increase in admissions related to the introduction of the 2nd SIGN guideline



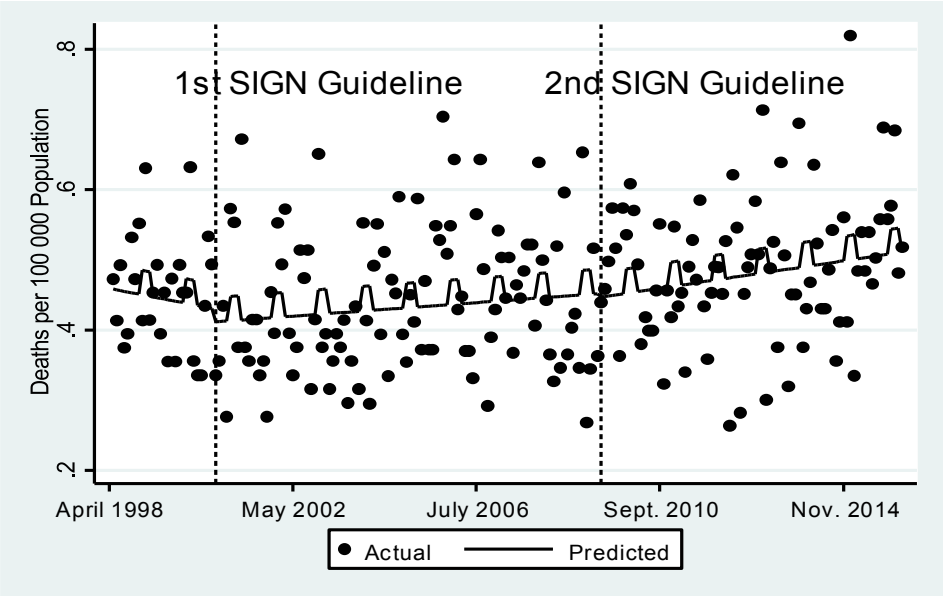
Appendix 9: The impact of the SIGN guidelines on the percentage of admissions for TBI that resulted in neurosurgery



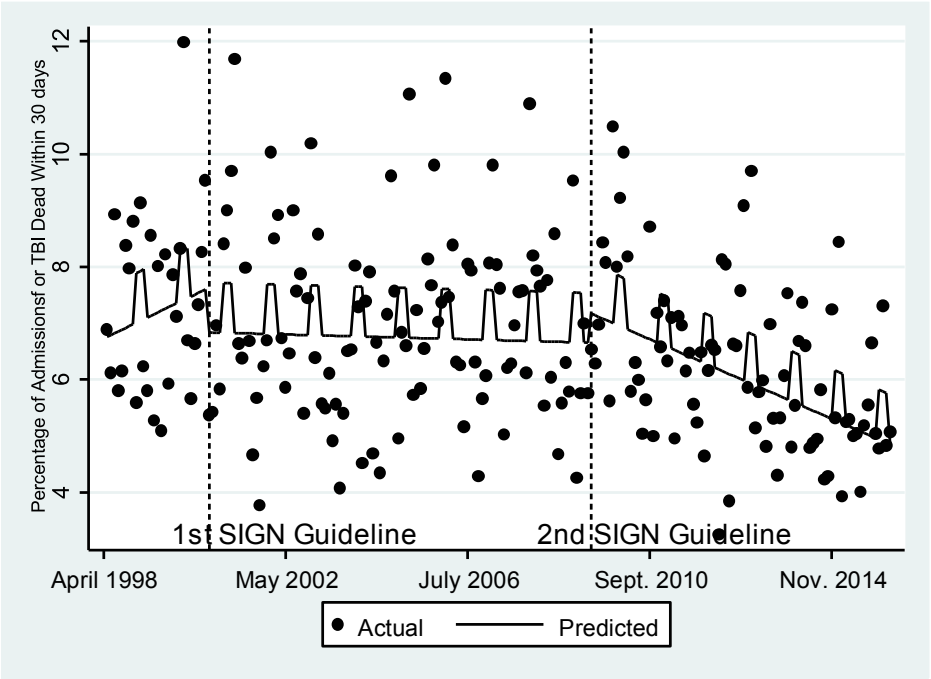
Appendix 10: Estimate of impact of the SIGN guidelines and 4-Hour Target on admissions for Traumatic Brain Injury with 12-month time lag

Outcome	**Initial Trend**	**1st SIGN Guideline**	**4-hour Target Introduced**	**2nd SIGN Guideline**	**Durbin-Watson Statistic**
Admissions for TBI/ 100 000	-0.05 (95% CI: -0.10 to 0.003) P=0.07	**Change level:** 0.75 (95% CI:-0.34 to 1.84) P=0.18	**Change level:** 0.35 (95% CI:-0.63 to 1.33) P=0.48	**Change level:** -0.16 (95% CI: -0.92 to 0.60) P=0.69	Untransformed 1.44 Prais-Winsten 2.03
		Change trend: 0.05 (95% CI:-0.02 to 0.12) P=0.16	**Change trend:** -0.01 (95% CI:-0.06 to 0.04) P=0.66	**Change trend:** 0.05 (95% CI:3 to 0.08) P<0.01	
Percentage TBI admissions neurosurgical	0.05 (95% CI: -0.01 to 0.11) P=0.10	**Change level:** -0.96 (95% CI:-2.19 to 0.28) P=0.13		**Change level:** 0.17 (95% CI:-0.59 to 0.93) P=0.66	Untransformed 1.85
		Change trend: -0.06 (95% CI:-0.12 to 0.003) P=0.06		**Change trend:** -0.02 (95% CI:-0.04 to-0.004) P=0.01	

Appendix 11: The impact of the SIGN guidelines on deaths per 100 000 population within 30 days of admission with traumatic brain injury



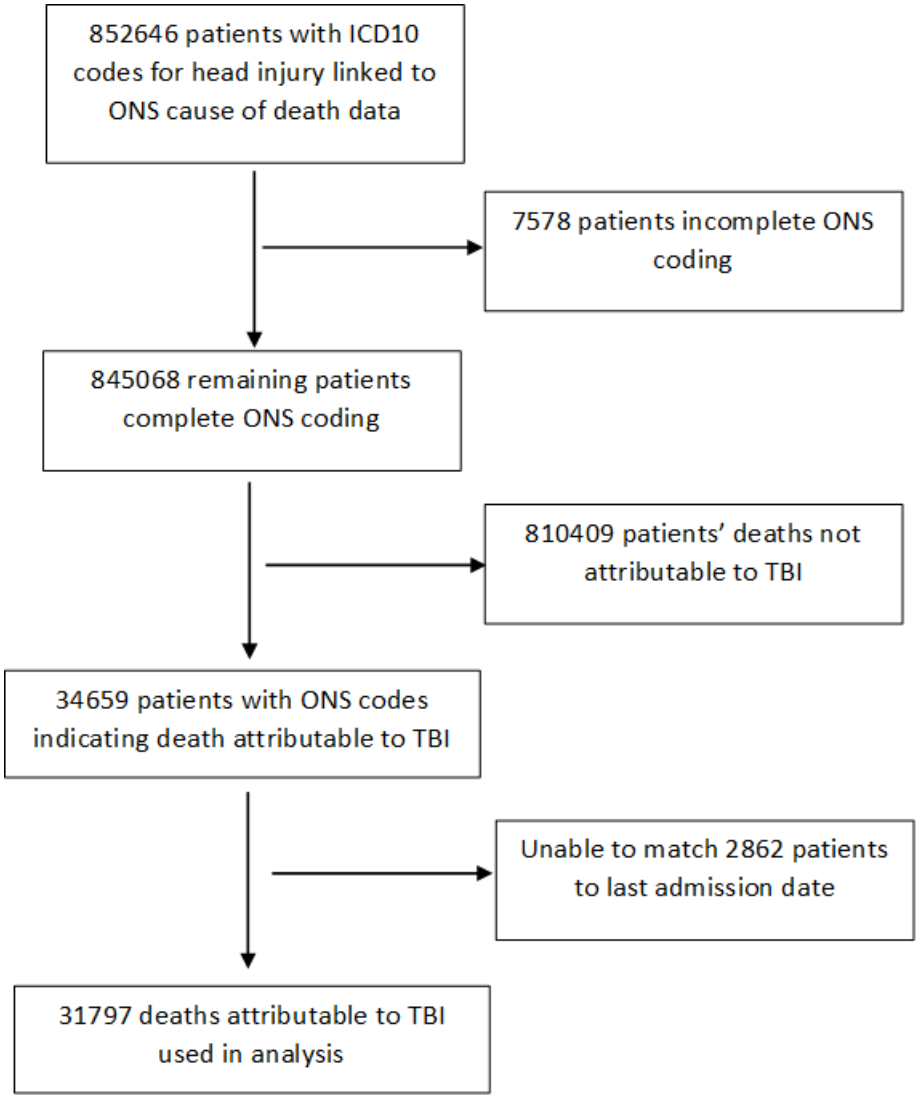
Appendix 12: The impact of the SIGN guidelines on the percentage of patients admitted with TBI who died within 30 days of admission



Appendix 13: Estimate of impact of the SIGN guidelines on deaths following admission for Traumatic Brain Injury with 12 month time lag

Outcome	**Winter**	**Initial Trend**	**1st SIGN Guideline**	**2nd SIGN Guideline**	**Durbin-Watson Statistic**
Deaths/100 000	0.03 (95% CI:- 0.01 to 0.06) P=0.15	-0.001 (95% CI:- 0.004 to 0.003) P=0.59	**Change level:** -0.02 (95% CI:- 0.09 to 0.06) P=0.66	**Change level:** -0.03 (95% CI:-0.08 to 0.03) P=0.32	Untransformed 2.29
			Change trend: 0.001 (95% CI:-0.002 to 0.005) P=0.44	**Change trend:** 0.001 (95% CI:- 0.0002 to 0.002) P=0.10	
Percentage TBI admissions death	0.74 (95% CI: 0.18 to 1.30) P=0.10	0.03 (95% CI:-0.03 to 0.10) P=0.34	**Change level:** -1.06 (95% CI: -2.40 to 0.29) P=0.12	**Change level:** -0.37 (95% CI:-1.20 to 0.47) P=0.39	Untransformed 2.17
			Change trend: -0.03 (95% CI:-0.10 to 0.04) P=0.38	**Change trend:** -0.02 (95% CI:-0.04 to -0.004) P=0.02	

Appendix 14: Flow diagram of identification of deaths attributable to TBI used in analysis



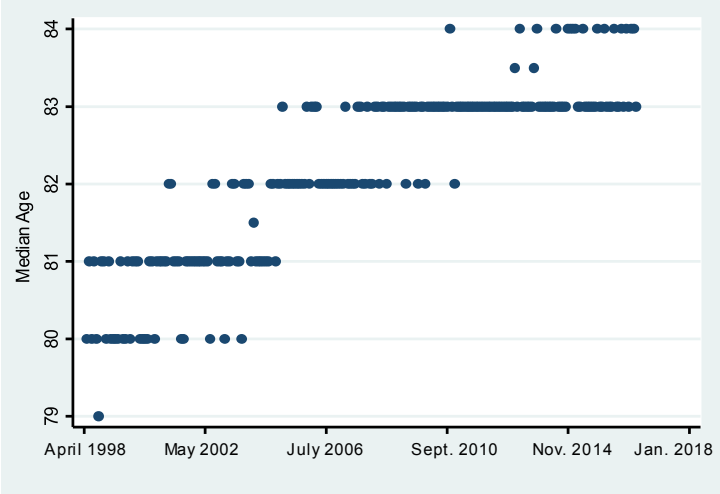
Appendix 15: Annual rate of deaths and admissions for TBI per 100 000 population in England (source NHS digital)

Year	Admissions 0-15	Admissions 16-64	Admissions 65+	Deaths 0-15	Deaths 16-64	Deaths 65+
*1998	177	288	98	0.45	3.96	4.27
1999	238	375	136	0.71	5.75	5.84
2000	218	357	132	0.69	6.32	6.75
2001	213	339	137	0.63	6.62	6.79
2002	198	327	132	0.47	6.44	8.04
2003	199	358	154	0.52	6.57	9.19
2004	207	417	187	0.50	7.12	9.20
2005	208	459	225	0.44	7.55	10.46
2006	201	472	242	0.50	7.57	11.38
2007	185	449	253	0.40	7.68	12.46
2008	177	420	266	0.26	6.84	12.56
2009	183	443	308	0.35	7.18	13.15
2010	181	409	325	0.29	6.19	14.71
2011	185	389	337	0.35	5.73	15.51
2012	162	336	330	0.27	5.80	16.28
2013	156	311	337	0.26	5.34	18.13
2014	151	302	366	0.15	4.84	19.77
2015	131	283	364	0.17	5.08	21.64
2016	125	255	359	0.28	5.17	21.70

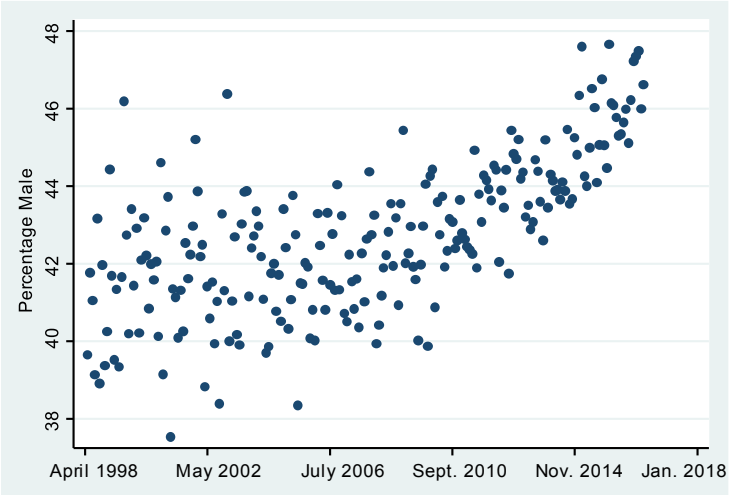
*Available data are from April 1998-March 2017, so 1998 is a part year and 2017 is not reported

Appendix 16: Monthly admission characteristics of patients with TBI:

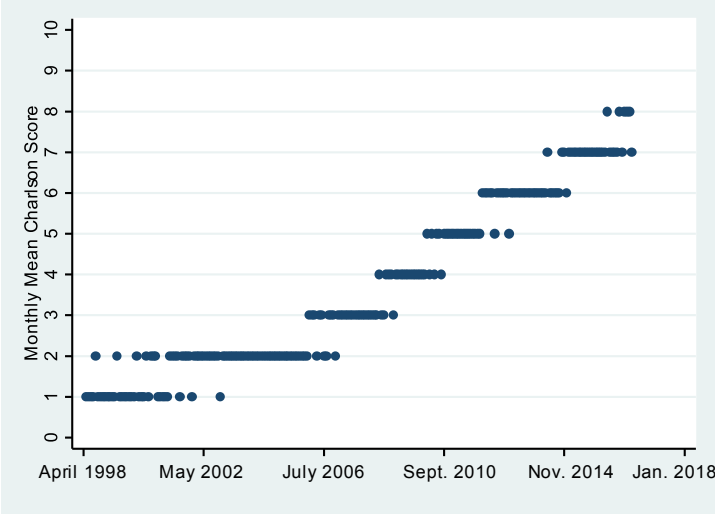
Median age (65 and over)



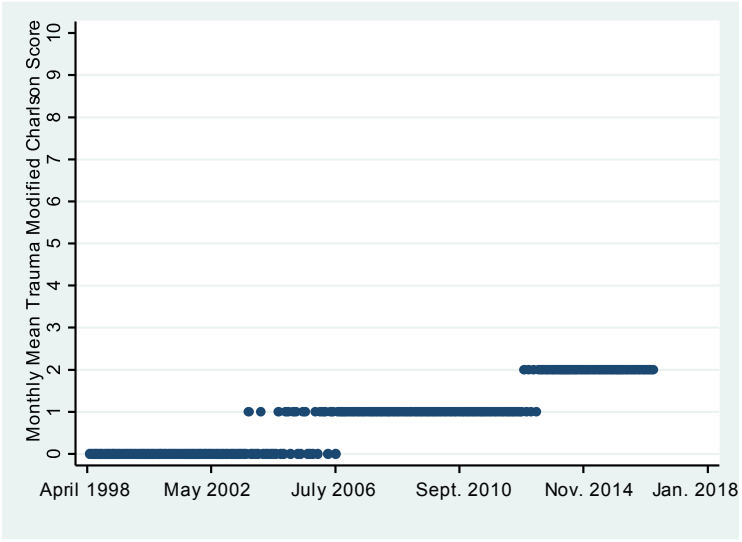
Proportion Male (65 and over)



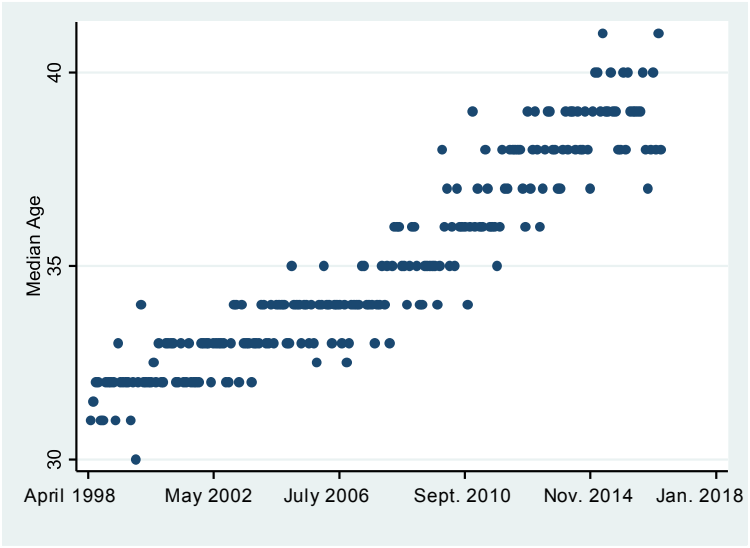
Mean Monthly Charlson Score (65 and over)



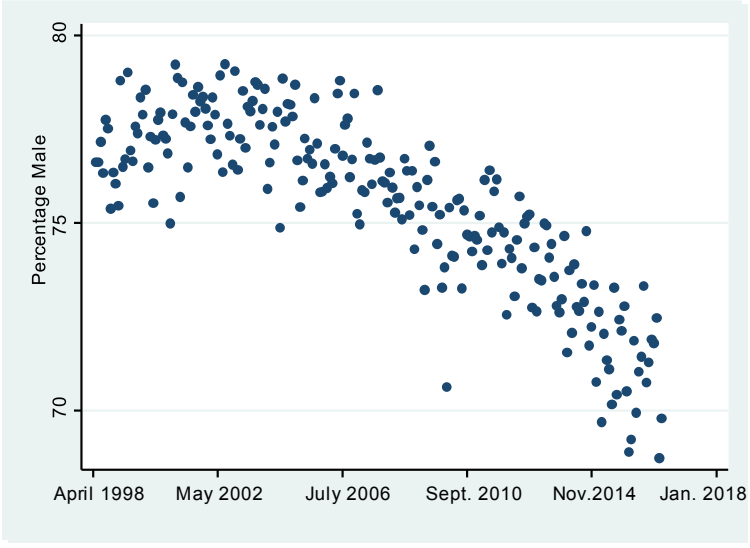
Mean Monthly Trauma Modified Charlson Score (65 and over)



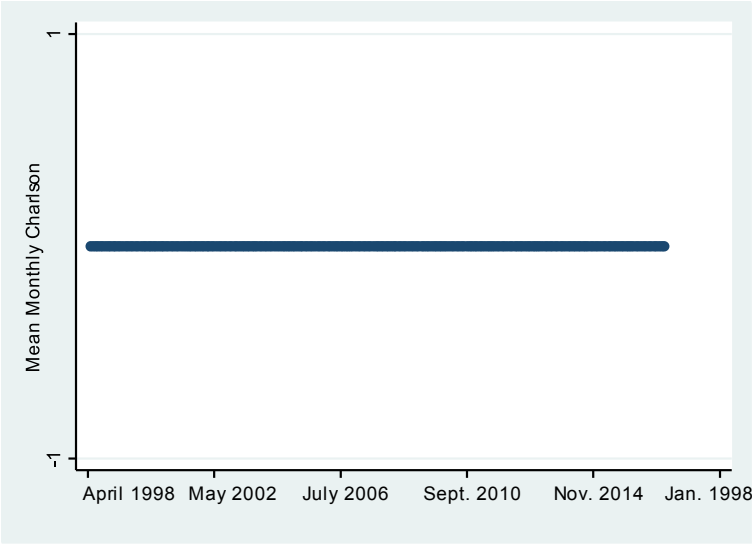
Median age (16-64)



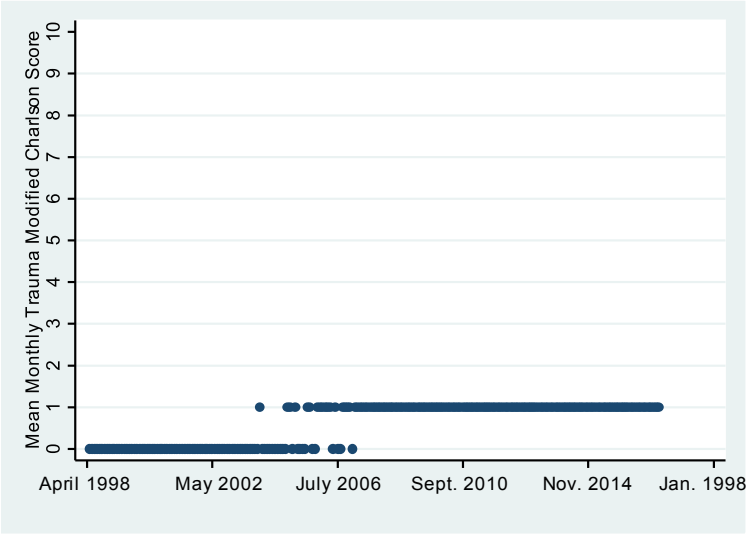
Proportion Male (16-64)



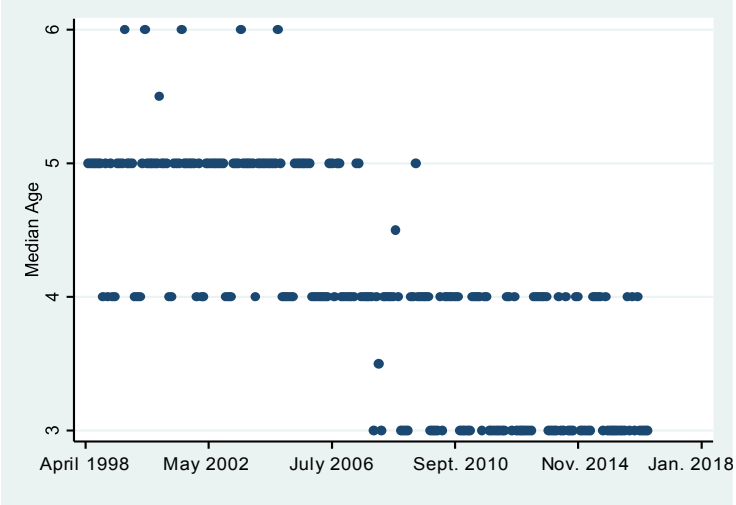
Mean Monthly Standard Charlson Score (16-64)



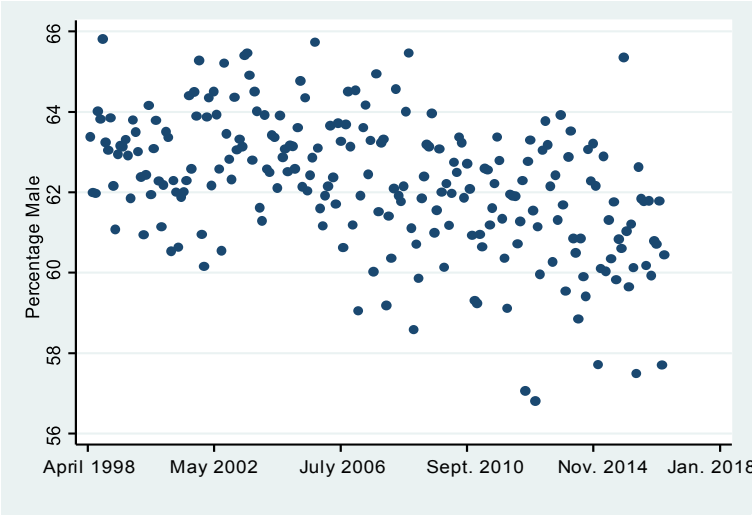
Mean Monthly Trauma Modified Charlson Score (16-64)



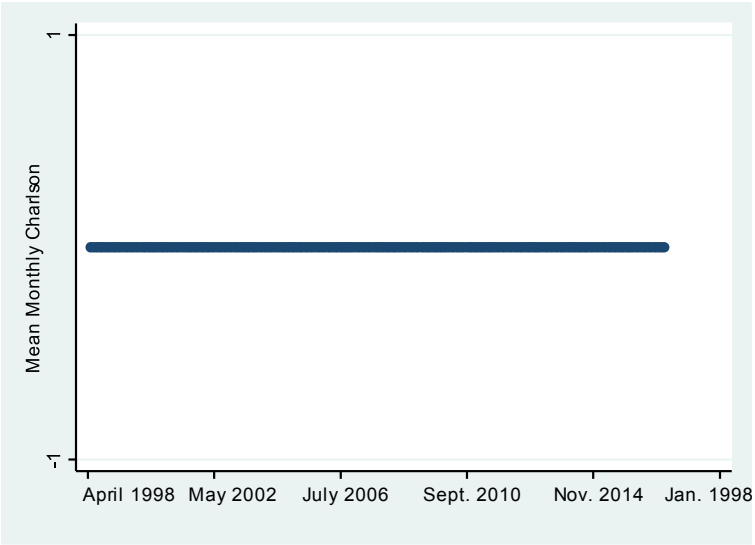
Median age (0-15)



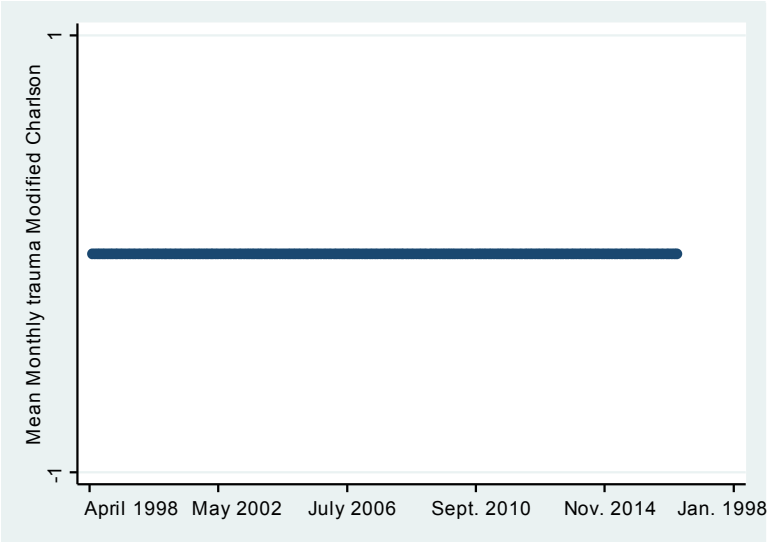
Proportion Male (0-15)



Mean Monthly Standard Charlson Score (0-15)

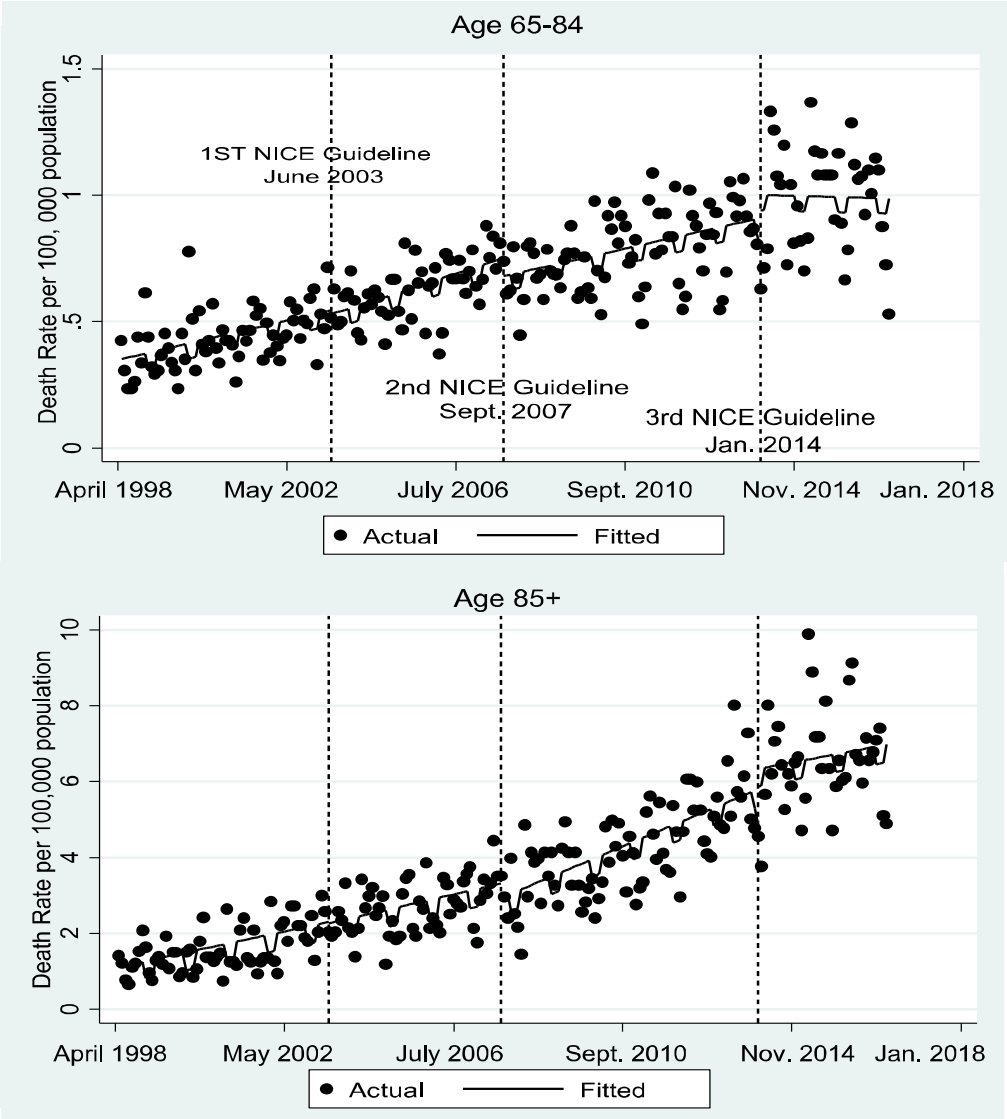


Mean Monthly Trauma Modified Charlson Score (0-15)



Appendix 17: Subgroup analysis of effect of the NICE guidelines on patients aged 65 deaths per 100, 000 population

Age Band	Winter Effect	Initial Trend	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline	Durbin-Watson Statistic
65-84	-0.06 (95% CI: -0.1 to -0.02) P=0.01	0.003 (95% CI: 0.001 to 0.005) P=0.006	**Change level:** -0.02 (95% CI:-0.13 to 0.1) P=0.78	**Change level:** -0.07 (95% CI: -0.19 to 0.04) P=0.21	**Change level:** 0.09 (95% CI:-0.03 to 0.21) P=0.15	Untransformed 1.62 Prais-Winsten 1.89
			Change trend: 0.001 (95% CI:-0.002 to 0.005) P=0.51	**Change trend:** -0.001 (95% CI: -0.005 to 0.002) P=0.44	**Change trend:** -0.003 (95% CI:-0.008 to 0.001) P=0.16	
85+	-0.46 (95% CI: -0.73 to -0.2) P<0.01	0.02 (95% CI: 0.01 to 0.03) P=0.01	**Change level:** -0.03 (95% CI:-0.7 to 0.7) P=0.92	**Change level:** -0.38 (95% CI: -1.05 to 0.29) P=0.27	**Change level:** 0.54 (95% CI:-0.18 to 1.26) P=0.14	Untransformed 1.68 Prais-Winsten 1.91
			Change trend: 0.001 (95% CI:-0.02 to 0.02) P=0.9	**Change trend:** 0.02 (95% CI: -0.001 to 0.04) P=0.65	**Change trend:** -0.02 (95% CI:-0.05 to 0.01) P=0.15	


Age 65-84
Death Rate per 100, 000 population
0
.5
1
1.5
1ST NICE Guideline
June 2003
2nd NICE Guideline
Sept. 2007
3rd NICE Guideline
Jan. 2014
April 1998
May 2002
July 2006
Sept. 2010
Nov. 2014
Jan. 2018
Actual
Fitted
Age 85+
Death Rate per 100,000 population
0
2
4
6
8
10
April 1998
May 2002
July 2006
Sept. 2010
Nov. 2014
Jan. 2018
Actual
Fitted

Appendix 18: The impact of the NICE head injury guidelines on monthly TBI mortality rate per 100 000 population adjusted for age, sex and comorbidity

Age Band	Winter Effect	Initial Trend	Median Age	Proportion Male	Charlson Score	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline	Durbin-Watson Statistic
65+	-0.1 (95% CI: -0.17 to -0.04) P<0.01	0.006 (95% CI: 0.002 to 0.009) P<0.01	-0.03 (95% CI: -0.09 to 0.02) P=0.25	0.03 (95% CI: -1.80 to 1.87) P=0.97	0.00003 (95% CI: -0.07 to 0.07) P>0.99	**Change level:** -0.04 (95% CI:-0.22 to 0.14) P=0.69	**Change level:** -0.1 (95% CI: -0.28 to 0.07) P=0.25	**Change level:** 0.14 (95% CI:-0.05 to 0.32) P=0.15	Untransformed 1.56 Prais-Winsten 1.86
						Change trend: 0.003 (95% CI: -0.003 to 0.008) P=0.39	**Change trend:** -0.0002 (95% CI:-0.006 to 0.005) P=0.95	**Change trend:** -0.005 (95% CI:-0.01 to 0.002) P=0.14	
16-64	-0.12 (95% CI: -0.15 to -0.09) P<0.01	0.001 (95% CI: -0.0003 to 0.003) P=0.1	0.03 (95% CI: 0.01 to 0.05) P<0.01	1.40 (95% CI:0.1 to 2.69) P=0.04	Not adjusted for as no change over time period.	**Change level:** -0.03 (95% CI:-0.11 to 0.06) P=0.52	**Change level:** 0.06 (95% CI:-0.14 to 0.02) P=0.15	**Change level:** -0.0004 (95% CI: -0.085 to 0.085) P=0.99	Untransformed 1.89 Prais-Winsten 1.98
						Change trend: 0.0001 (95% CI: -0.002 to 0.004) P=0.52	**Change trend:** *-0.006 (95% CI: -0.008 to -0.003) P<0.01*	**Change trend:** 0.003 (95% CI: 0.00005 to 0.007) P=0.047	
0-15	-0.01 (95% CI: -0.01 to 0.001) P=0.09	-0.0002 (95% CI: -0.0005 to -0.00002) P=0.04	0.006 (95% CI: 0.00002 to 0.01) P=0.049	-0.09 (95% CI:-0.28 to 0.09) P=0.32	Not adjusted for as no change over time period.	**Change level:** 0.0001 (95% CI: -0.01 to 0.01) P= 0.99	**Change level:** -0.0004 (95% CI: -0.01 to 0.01) P=0.95	**Change level:** -0.01 (95% CI:-0.03 to 0.001) P=0.08	Untransformed 2.19 Prais-Winsten 1.99
						Change trend: 0.0001 (95% CI:-0.0003 to 0.0005) P=0.58	**Change trend** 0.00005 (95% CI:-0.0003 to 0.0004) P=0.81	**Change trend:** 0.0004 (95% CI: -0.00007 to 0.001) P=0.09	

Appendix 19: Sensitivity analysis of implementation lags on the impact of the NICE head injury guidelines on deaths per 100 000 population

Age Band	Winter Effect	Initial Trend	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline	Durbin-Watson Statistic
65+	-0.11 (95% CI: -0.18 to-0.04) P<0.01	0.005 (95% CI: 0.001 to 0.008) P<0.01	**Change level:** -0.007 (95% CI:-0.2 to 0.19) P=0.95	**Change level:** -0.05 (95% CI: -0.25 to 0.14) P=0.60	**Change level:** 0.13 (95% CI:-0.06 to 0.33) P=0.18	Untransformed 1.56 Prais-Winsten 1.86
			Change trend: 0.005 (95% CI:-0.003 to 0.012) P=0.24	**Change trend:** -0.0018 (95% CI: -0.01 to 0.006) P=0.65	**Change trend:** -0.006 (95% CI:-0.01 to 0.002) P=0.16	
16-64	-0.1 (95% CI: -0.14 to -0.06) P<0.01	0.002 (95% CI:0.001 to 0.004) P<0.01	**Change level:** 0.01 (95% CI: -0.08 to 0.11) P=0.78	**Change level:** 0.06 (95% CI:-0.15 to 0.003) P=0.11	**Change level:** 0.006 (95% CI: -0.09 to 0.1) P=0.91	Untransformed 1.75 Prais-Winsten 1.94
			Change trend: -0.001 (95% CI: -0.004 to 0.003) P=0.77	**Change trend:** -0.004 (95% CI:-0.008 to -0.001) P=0.03	**Change trend:** 0.002 (95% CI:-0.002 to 0.005) P=0.41	
0-15	-0.01 (95%CI:-0.01 to -0.001) P=0.02	-0.0003 (95% CI: -0.0005 to -0.00001) P=0.03	**Change level:** 0.001 (95% CI: -0.01 to 0.01) P= 0.88	**Change level:** -0.001 (95% CI: -0.01 to 0.01) P=0.93	**Change level:** -0.01 (95% CI:-0.03 to 0.002) P=0.097	Untransformed 2.18 Prais-Winsten 1.98
			Change trend: 0.00007 (95% CI: -0.0006 to 0.0005) P=0.80	**Change trend** 0.0002 (95% CI: -0.0003 to 0.0007) P=0.47	**Change trend:** 0.0005 (95% CI: -0.00003 to 0.001) P=0.07	

Appendix 20: Sensitivity analysis of implementation lags on the impact of the NICE head injury guidelines on admissions per 100 000 population

Age Band	Winter Effect	Initial Trend	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline	Durbin-Watson Statistic
65+	-0.51 (95% CI: -1.05 to 0.04) P=0.07	0.02 (95% CI -0.02 to 0.05) P=0.31	**Change level:** 3.88 (95% CI: 2.11 to 5.66) P<0.01	**Change level:** 1.71 (95% CI: -0.08 to 3.5) P=0.06	**Change level:** 0.6 (95% CI:-1.17 to 2.36) P=0.51	Untransformed 1.24 Prais-Winsten 2.05
			Change trend: 0.17 (95% CI: 0.09 to 0.24) P<0.01	**Change trend:** -0.1 (95% CI: -0.17 to -0.03) P=0.01	**Change trend:** -0.1 (95% CI:-0.18 to -0.03) P=0.01	
16-64	-2.16 (95% CI: -3.03 to -1.28) P<0.01	-0.08 (95% CI:-0.12 to -0.03) P<0.01	**Change level:** 8.6 (95% CI: 6 to 11.2) P<0.01	**Change level:** -2.22 (95% CI:-4.84 to 0.4) P=0.1	**Change level:** 0.25 (95% CI:-2.33 to 2.84) P=0.85	Untransformed 1.49 Prais-Winsten 2.06
			Change trend: 0.2 (95% CI: 0.09 to 0.3) P<0.01	**Change trend:** -0.32 (95% CI: -0.42 to -0.21) P<0.01	**Change trend:** 0.06 (95% CI:-0.05 to 0.16) P=0.29	
0-15	-2.93 (95% CI: -3.49 to -2.38) P<0.01	-0.06 (95%CI:-0.11 to -0.01) P=0.02	**Change level:** 1.16 (95% CI: -1.22 to 3.54) P= 0.34	**Change level:** 0.4 (95% CI: -1.99 to 2.8) P=0.74	**Change level:** 0.5 (95% CI:-1.87 to 2.88) P=0.68	Untransformed 1.06 Prais-Winsten 1.71
			Change trend: 0.02 (95% CI: -0.1 to 0.13) P=0.8	**Change trend** -0.01 (95% CI: -0.12 to 0.1) P=0.9	**Change trend:** -0.06 (95% CI: -0.17 to 0.05) P=0.28	

Appendix 21: Annual attendance to the ED in England for head injury

Year	Number head injury primary diagnosis for ED attendance	Proportion attendances primary diagnosis head injury (all attendances)	Proportion attendances primary diagnosis head injury (where primary diagnosis known)
2007/2008	238,099	1.90%	
2008/2009	272,485	2.00%	
2009/2010	336,396	2.2%	3.7%
2010/2011	363,187	2.2%	3.8%
2011/2012	421,221	2.4%	3.8%
2012/2013	423,413	*2.3%*	*3.7%*
2013/2014	449,397	*2.4%*	3.8%
2014/2015	395, 401	*2%*	3.1%
2015/2016	430, 725	*2.1%*	3.2%
2016/2017	449, 584	*2.2%*	3.3%
2017/2018	443, 758	*2.1%*	3.0%

*data obtained from NHS Digital Annual ED reports https://digital.nhs.uk/data-and-information/publications/statistical/hospital-accident--emergency-activity (data was submitted by all hospitals in England from 2012 onwards, prior to this data was only submitted by a variable proportion of hospitals)

Appendix 22: Full Search Strategy

Embase search 24/11/2016 1996 to 2016 Week 47:

12	1 and 10 and 11	3167
11	2 or 3 or 4 or 5 or 6 or 9	104649
10	7 or 8	2298555
9	"cerebral contusion".mp. or exp brain contusion/	2627
8	exp outcome variable/ or outcome.mp. or exp critical care outcome/ or exp adverse outcome/	1787765
7	exp prognosis/ or prognos*.mp.	704898
6	exp subarachnoid hemorrhage/ or "traumatic subarachnoid h#em*".mp.	28977
5	"extradural h#em*".mp.	225
4	exp epidural hematoma/ or "epidural h#em*".mp.	4775
3	exp subdural hematoma/ or "subdural h#em*".mp.	10281
2	exp Intracranial Hemorrhages/ or "intracranial h#em*".mp.	92720
1	"traumatic brain injury".mp. or traumatic brain injury/ or head injury/	69888

MEDLINE **Ovid MEDLINE(R) without Revisions** 1996 to November Week 3 2016

24/11/2016

9	1 and 7 and 8	1143
8	2 or 3 or 4 or 5 or 6	34984
7	exp Risk Factors/ or risk.mp. or exp Risk/ or exp Risk Assessment/	1502469
6	"traumatic subarachnoid h#emorrhage".mp. or exp Subarachnoid Hemorrhage, Traumatic/	231
5	exp Cerebral Hemorrhage, Traumatic/ or exp Hematoma, Epidural, Cranial/ or "extradural haemorrhage".mp.	1434
4	exp Hematoma, Subdural/ or "subdural h#em*".mp.	3712
3	exp Intracranial Hemorrhages/ or "intracranial h#em*".mp.	34253
2	exp Cerebral Hemorrhage/ or "intracerebral h#em*".mp.	14418
1	"head injury".mp. or exp Craniocerebral Trauma/	75438

CINHAL plus access through EBSCO 24/11/2016 1983-2016:

Search Terms	Search Options	
S11	((S3 OR S4 OR S5 OR S6) AND (S3 OR S4 OR S5 OR S6 OR S7)) AND (S8 AND S9 AND S10)	View Results (292)
S10	(S3 OR S4 OR S5 OR S6) AND (S3 OR S4 OR S5 OR S6 OR S7)	View Results (6,995)
S9	S1 OR S2	View Results (17,827)
S8	prognosis or outcome	View Results (592,464)
S7	brain contusion OR cerebral contusion	View Results (106)
S6	extradural haematoma OR extradural hematoma OR (epidural hematoma or epidural hemorrhage)	View Results (753)
S5	intracerebral hemorrhage OR intracerebral haemorrhage OR intracerebral bleed	View Results (2,456)
S`4	intracranial hemorrhage OR intracranial haemorrhage OR intracranial hematoma OR intracranial haematoma	View Results (3,176)
S3	subdural hematoma OR subdural hemorrhage OR subdural haematoma OR subdural haemorrhage	View Results (1,246)
S2	traumatic brain injury	View Results (10,081)
S1	head injury	View Results (7,746)

Cochrane CENTRAL:

Search Name: Prognostic systematic Review

Date Run: 24/11/16 11:33:55.251

ID	Search	Hits
#1	Craniocerebral Trauma	417
#2	head injury	2563
#3	#1 or #2	2704
#4	Hematoma, Subdural	228
#5	Hematoma, Epidural, Cranial	20
#6	Cerebral Hemorrhage	2609
#7	Skull Fracture	130
#8	Skull Fracture, Basilar	6
#9	Skull Fracture, Depressed	13
#10	brain contusion	131
#11	#4 or #5 or #6 or #7 or #8 or #9 or #10	2969
#12	#3 and #11	211

All Results (211)

○ Cochrane Reviews (138)

◉ All ○ Review ○ Protocol

○ Other Reviews (4) ◉ Trials (63) ○ Methods Studies (0) ○ Technology Assessments (0) ○ Economic Evaluations (1) ○ Cochrane Groups (5)

Only trials retrieved.

Appendix 23: Data Extracted from Included Studies

Studies Only Included in Meta-Analysis of Prevalence of Outcomes N=26

Reference	Population	Study Design	Outcome Measures	Prognostic factors assessed	Results	Quality Appraisal
Nishijima et al 2013 Sacromento USA Variability of ICU Use in adult patients with minor traumatic intra-cranial haemorrhages	Multicenter-8 sites Western USA. All Level 1 Trauma registries searched for ICD-9 codes intra-cranial haemorrhage 2005-2010 Inclusion Criteria: • Age ≥ 18 years • Traumatic ICH • Initial ED GCS 15 • ISS less than 16	Retrospective Cohort Study Objective: 1) assess the variability of ICU use in a cohort of patients with minor traumatic intra-cranial haemorrhages across multiple trauma centres. 2)Estimate the proportion of minor traumatic intracranial haemorrhages patients admitted to ICU that do not receive an ICU intervention	Initial ICU admission from ED Proportion of patients receiving crit care intervention defined as: Neurosurgical intervention Mechanical ventilation Vasopressor/ionotropic use Transfusion blood product Invasive monitoring	Age Initial GCS Initial BP LOS hosp ICU stay Procedures as coded in trauma registry AIS	11240 patients coded as bleeds 771 excluded due to missing data 1412 remaining met inclusion criteria. 888/1412 admitted ICU, significant variation between sites 44/1412 (3.1%) had critical care intervention 6/1412 neurosurgical intervention 847/888 patients admitted ICU no crit care intervention Mean/median GCS=15 Mean/median age= 48	**Study Recruitment: Mod risk bias** Dependent on accuracy on recording on trauma registry. Does have some quality assessment of data imputation Note initial GCS 15- lower risk group **Attrition: Low risk** Follow up only during hospital admission **Prognostic factor measurement: Low risk** Doesn't really apply as testing disposition not outcomes **Outcome measures: Low risk** No measure of outcomes after discharge, but study primarily about disposition. Does not report deaths. **Confounding Factors:** States IIS increases ICU admission- will be related to other injuries **Statistical techniques: low risk** N/A **Overall** Only GCS15 patients with low ISS.
Nishijima et al 2015 Sacromento USA Long-term Neurological	Level1 trauma centre 2008-2013 Inclusion Criteria: • Age ≥ 18 years • Identified ICH ICD9 code trauma registry • Initial ED GCS 15	Retrospective Cohort Study Aim compare long-term neurological outcomes in low- risk patients with traumatic intracranial hemorrhage (tICH) admitted to the ICU	Prospective long term outcome measure at 6 months Either GOS-E 8 fully recovered or GOS-E 1-7 not fully recovered	age sex, mechanism of injury initial ED GCS score, initial (SBP) heart rate, respiratory rate, blood alcohol level, AIS score	188 met inclusion criteria 151/188 complete data= cohort 106 admitted ICU (70%) 45 admitted ED (30%) 1/151 patients neurosurgical intervention as inpatient 1/151 patient died as inpatient 78 (52%) GOS-E 8 at 6 months	**Study Recruitment: Mod risk bias** Dependent on accuracy on recording on trauma registry and accuracy of case notes. Low risk group- GCS 15 and benign CT **Attrition: Low risk** Loss of 37 patients to follow up **Prognostic factor measurement: Low risk**

Outcomes in Adults with Traumatic Intracranial Hemorrhage Admitted to ICU versus Floor	• Isolated Head Injury based on AIS score • Age<65 • No evidence midline shift CT • Present on TBI data base due to suspected TBI/evidence of ICH	(intensive care unit) versus patients admitted to the floor.		ISS score INR Rotterdam CT score	Does present analysis for outcome at 6 months GOSE but no inpatient measures of deterioration. Adjusted analysis, floor admission versus ICU had an odds ratio of 0.77 (95% CI [0.36-1.64]) for a GOS-E score of 8 at six months. Mean/median GCS=15 Mean/median age= 40	As recorded in case notes so dependent on accuracy **Outcome measures: Low risk** Prospective follow up by trained staff using validated tool. Not clear what would happen to patients who died or deteriorated and attended a different hospital. **Confounding Factors:** Patients which are perceived as higher risk will be put on ICU, likely to be differences in comorbidities **Statistical techniques: low risk** Well presented- not really relevant to meta-analysis Only GCS15 patients with benign looking CT scans
Schaller et al 2015 Switzerland	Level 1 Trauma centre Bern Switzerland Jan 2006-Dec 2007 Inclusion criteria: • Admission GCS 13-15 • Observed for 24H • Localised intra-cranial bleeds up to 5mm- this is from the CCHR paper Exclusion Criteria: • Bleeds > 5mm maximum diameter • Multiple bleeds • History of bleeding tendency • Anti-coagulant or anti-platelet medication • Intoxication	Retrospective cohort study/case series Aim to assess if a specific group of patients with small bleeds can be discharged from hospital without 24 hours of observation	Deterioration in neurological status or need for neurosurgery.	Prognostic factors are the inclusion/exclusion criteria No comparison in risk of deterioration in 2 groups.	110 patients met inclusion and exclusion criteria. None deteriorated within the period of hospital observation, required neurosurgery or re-attended. Mean/median GCS=14.6 Mean/median age= 40 Percent anticoagulated=0	**Study Recruitment: Low risk bias** Retrospective cohort review- reliant on accuracy of written notes. **Attrition: Mod risk** Patients may have moved out of catchment area of hospital without the researchers being aware. Loss to F/U if re-presented different hospital. **Prognostic factor measurement: Mod risk** Reliability of case notes- may be incomplete Interpretation size of the bleed was taken from written radiology report ?reliability. **Outcome measures: Moderate risk** Study dependent on patients re-presenting at the same hospital following discharge if had delayed deterioration. Not clear how patients died in the community would have been identified. **Confounding Factors: Low risk** No obvious confounding factors

	• Other injuries • Live alone • Live greater the 1H from hospital					Cohort selection criteria including not living alone may select out high risk older patients. Statistical techniques: N/A **General comments:** Mean age 39.9 years and 25% caused by sporting injuries. ?Age as the confounding low risk prognostic factor. Not generalizable to older populations Small numbers
Levy et al 2011 Colorado USA	Level 1 Trauma centre Denver USA Jan 1998-Dec 2008 Inclusion criteria: • Admission ED GCS 13-15 • On trauma registry • Blunt head trauma • ICD 850-850.99- consistent with concussion (i.e. no detected injury by CT) • Admitted to hospital • AIS score 2 before 2008 or 1 / 2 in 2008 • IC9 code for SAH Exclusion Criteria: • Patient admitted directly to hospital • Multiple injuries AIS score >1 head or other regions • Age less than 18 • Not admitted	Retrospective Cohort Study **Aim** To assess whether patients admitted with CT –VE mTBI have different outcomes to patients with mTBI and traumatic SAH Univariate and multivariate regression used to examine covariates and relationship to outcomes	ED disposition ICU admission Neurosurgery In-hospital mortality Progression of SAH on CT	Age (18-39)(40-69)(70+) Transfer status Cause of injury GCS Blood alcohol level Presence of skull fracture CT report- divided into small/medium/large based on language included in report	1144 patients admitted with mTBI but negative CT scan 117 with mTBI and traumatic SAH 1/117- progression on repeat CT scan 0/117 required neurosurgical intervention 1/117 died (progression on CT) 4/1144 died All patients died >70 **Logistic regression model tSAH versus concussion** ICU admit adjusted OR 8.87 (5.62-14.02) P<0.0001 ICU LOS>1D OR0.29 (0.11-0.74) P=0.01 Hosp LOS>1D OR1.07 (0.67-1.69) P=0.79 Mortality OR2.46 (0.27-22.17) P=0.42 Discharge to rehab Age18-39 OR5.48 (0.25-121.70) P=0.28 Age 40-69 7.96 (1.91-33.11) P=0.004 Age >70 1.33 (0.50-3.53) P=0.56	**Study Recruitment: Low risk bias** Patients recruited from trauma registry depends on how good this is Only admitted patients- higher acuity patients then discharged. Likely patients admitted for other reasons if CT negative TBI (although excludes other injuries). **Attrition: Low risk** All inpatient outcomes **Prognostic factor measurement: Mod risk** CT findings abstracted from CT reports- severity assigned by language- not actually used in regression model **Outcome measures: Moderate risk** Only inpatient outcomes- possibility of discharge and deterioration. **Confounding Factors: High risk** Patients admitted with CT negative TBI likely to be frail or have other reasons for admission- this will affect outcome measures compared to SAH patients admitted due to +ve CT. **Statistical techniques: Low risk** Well presented.

						Can use for pooling for outcomes SAH- supports low risk sub-population
Levy et al 2014 USA	Level III rural non-neurosurgical unit in Rocky mountains April 2007-Dec 2012 April 2007 patients with small bleeds selectively not transferred to neurosurgical unit Inclusion criteria: • Admission GCS 13-15 • CT positive intra-cranial injury • Not transferred to neurosurg unit in accordance with non-transfer policy. • CT findings of small SAH • Punctate or minimal contusion • Punctate or minimal intra-cranial bleed	Retrospective cohort Study Aim Investigate outcomes after a novel non-transfer policy for mTBI patients with small ICH introduced in a small rural trauma unit without neurosurgical cover	Length of stay Mortality Neurological deterioration Neurosurgery Re-admission in 90 days of discharge Inter-hospital transfer Need for repeat CT	No comparison to patients that were transferred	76/273 patients not transferred >50% injuries due to skiing/snow boarding 71% patients less then 55 No patient deteriorated, died or required neurosurgery or required delayed transfer whilst admitted to hospital. 2 patients re-admitted within 90 days- 1 patient 6 weeks following admission developed an acute on chronic subdural- drained. 1 patient re-admitted with unrelated complaint. Mean/median GCS=14.7 Mean/median age= 36 Percent anticoagulated=0	**Study Recruitment: Low risk bias** Retrospective cohort review- reliant on accuracy of written notes. CT inclusion criteria are subject and patients may have been transferred despite meeting non-transfer policy if clinicians were concerned. **Attrition: low risk** Prognostic factor measurement: Mod risk Reliability of case notes- may be incomplete The definitions of bleed size are subjective. **Prognostic Factors** N/A **Outcome measures: Moderate risk** Study dependent on patients re-presenting at the same hospital following discharge if had delayed deterioration. **Confounding Factors: Low risk** Age affect outcome and size of bleed **Statistical techniques: N/A**

	• Small SDH, no mass effect Exclusion Criteria: • Any coagulopathy • Basilar skull fracture or evidence of CSF leak • Extra-dural bleed • Any significant contusion or SDH/intra-cerebral haemorrhage Review and discussion of CT and patient with neurosurgeon if unsure if should be transferred					**General points** Small numbers. No comparator group- need to compare to transferred patients outcomes. Patient not generalizable- v. young and atypical mechanism of injury (mostly winter sports related). Likely that any patient clinicians felt risky would have been transferred even if did not meet transfer criteria- no way to check this.
Joseph et al 2013 USA The acute care surgery model: Managing traumatic brain injury without an inpatient neurosurgical consultation	Level 1 Trauma centre 2009-2011 (likely subset of patients presented below) Inclusion criteria: • GCS13-15 • Trauma • Positive findings CT- skull fracture and/or ICH Exclusion Criteria: • Pre-hospital anti-platelets or anti-coagulants	Retrospective cohort study- propensity matching 1:2 ratio patients managed solely by trauma surgeons versus patients that had neurosurgical consultation. **Hypothesis** Trauma surgeons can manage mTBI patients with CT detected intra-cranial haemorrhage without neurosurgical invlolvement	Hospital admissions ICU admissions Neurosurgical interventions ED visits after discharge Mortality Progression on CT imaging	Age Sex Initial GCS ISS Head-abbreviated injury score Neurological examination CT scan findings-type of skull fracture/type of ICH/size of bleed-reviewed by study investigator	404-GCS13-15 patients with CT detected injuries in study period. 270/404 used for this study 90/270- had neurosurgical consultations (NC) 180 no neurosurgical consultation. (no-NC) Whether neurosurgical consultation requested as discretion of non-specialist surgeon. Propensity matching in this study between 2 groups. 0/270 neurosurgical interventions, hospital mortality or readmissions either group. 78/90 no-NC and 158/180 NC admitted hospital (P=0.8) 18/90 no-NC and 80/180 NC admitted ICU (P=0.001) Routine repeat CT 18/90 no-NC 155/180 NC (P<0.001) No progression on any repeat CT 8% no-NC and 4% NC group re-attended ED. No readmissions. Mean/median GCS=15 Mean/median age= 30	**Study Recruitment: High risk bias** Subset of patients that meet inclusion criteria selected in order to facilitate propensity matching. Possible selection out of higher acuity patients as these will have al been referred to a neurosurgeon. **Attrition: low risk** In patient outcomes and documented ED re-attendances- low risk of patients being lost to follow up **Prognostic factor measurement: Low risk** All routinely collected clinical data apart from CT imaging which re-reviewed. **Outcome measures: Mod risk** Study dependent on patients re-presenting at the same hospital following discharge if had delayed deterioration. **Confounding Factors: Mod risk** Does not exclude patients with additional injuries

					Percent anticoagulated=0	**Statistical techniques: High risk** Does not outline how matched groups using propensity scoring General points Small numbers. Likely reporting data reported else where.
AbdelFattah et al 2012 USA	Level 1 trauma center Dallas Texas Prospective recruitment 2010-2011 Inclusion criteria: • Adult with ICH (note doesn't explicitly state 2ndary to trauma- but implied) Excluded: • Age<16 • GCS<13 • Undergone planned or immediate neurosurgery • Transferred patients	Prospective Cohort Study Hypothesis: Repeat CT imaging in GCS13-15 with ICH, without neurological progression, does not impact the need for neurosurgical intervention. Patients divided into those 2 groups. Patients with planned repeat CT imaging and those with CT imaging if deteriorated. Allocation by neurosurgeon-no deviation from normal practice.	Outcome measures during hospital admission: Neurologic progression. Medical intervention Neurosurgical intervention Repeat CT imaging- worse CT defined as worse by a blinded radiologist/neurosurgeon giving qualitative measure of bleed.	Comparison between groups: Age Sex Coagulation status Anti-platelets ISS GCS	145 patients met inclusion/exclusion criteria. 92/145 for routine repeat CT 53/145 for CT if deteriorated Selective group more likely aspirin use P=0.02 Routine repeat CT worse Head AIS score (P<0.001) Otherwise groups comparable 5/53 deteriorated and had a repeat CT + 1/53 had repeat scan as started on warfarin 1/145 patients died (due to other injuries) 27/145 radiological deterioration 9/145 patients intubated- states for other injuries Mean/median GCS=14.5 Mean/median age= 41 Percent anticoagulated=6	**Study Recruitment: low risk** Prospective recruitment- states recruited all eligible patients. Doesn't explain how recruitment occurred. **Attrition: low risk** Follow up only for period in hospital **Prognostic factor measurement: Low risk** Blinded appraisal of CT scans by researcher. **Outcome measures: Mod risk** No F/U following discharge- missed delayed outcomes, could have looked for re-attendance. Doesn't report neurosurgical outcome measures. **Confounding Factors: High risk** Not isolated head injury- other injuries have clearly affected outcome measures **Statistical techniques: Low risk** None Small study with confounders regarding outcomes.
Nayak et al 2013 USA	University Hospital Newark New Jersey Level 1 trauma centre 2003-2008 Inclusion criteria: • Aged 18 and over	Retrospective Chart Review Aim: To compare neurologic outcomes of MHI patients with an intra-cranial bleed with a normal neurological	Neurosurgical intervention after 24 hours- craniotomy, ventriculostomy, ICP bolt/measurement Death in hospital Discharge disposition	Age Sex Mechanism of Injury GCS on arrival ISS HAIS	321/864 patients GCS13-15 with ICB met inclusion criteria 20% excluded because incomplete medical notes/transfers 0/321 neurosurgical intervention-all within 24 hours of admission No deaths	**Study Recruitment: Low risk** Retrospective case note review- depends on information being recorded correctly. **Attrition: Mod risk** 20% excluded because of incomplete notes **Prognostic factor measurement: Mow risk**

	• Blunt trauma • Intra-cranial bleed • Admitted to hospital • GCS13-15 on arrival to ED • GCS 15 24 hours after attendance to ED Excluded: • History brain disease, e.g. dementia • Previous brain injury e.g. CVA • Liver cirrhosis, renal disease, coronary artery disease, bleeding or clotting disorder • Unable to assess GCS due to drugs e.g. sedation/intubation • Neurological deterioration leading to repeat CT • Aged less than 15 • Incomplete notes	examination managed with and without a repeat CT head scan	LOS hospital GOS at f/u clinic/ re-attendance if applicable	GCS and neurological examination every 2 hours- routine care on a flow sheet	19/142 worse CT on repeat CT after 24 hours of admission 179/321 single CT 142/321 routine repeat CT 76/321 returned to F/U clinic- uneventful 14/321 returned to ED due to symptoms. Mean/median GCS=14.9 Mean/median age= 41	Neuroradiology reports taken at face value- no verification **Outcome measures: mod risk** No uniform follow up of patients post discharge. Some patients had F/U clinic others didn't. Patients may presented after discharge to other sites. **Confounding Factors: low risk** None obvious **Statistical techniques: Low risk** None completed The inclusion/exclusion criteria have selected out all patients that are not GCS 15 at 24 hours. Different population than all GCS 13-15 patients with TBI on CT- probably unable to pool this data. Does show patients that are GCS 15 at 24 hours low risk.
Anandalwar et al 2016 New Jersey USA	University Hospital Newark New Jersey Level 1 trauma centre 2009-20012 Inclusion criteria: • Aged 18 and over • Blunt trauma • Intra-cranial bleed/skull fracture • Admitted to hospital	Retrospective cohort study **Aim** Assess the outcomes following the implementation of a policy of observation only (no repeat CT imaging) for GCS 15 patients	Repeat CT after 24 hours of admission due to clinical concern or deterioration. Progression on any repeat CT completed. Neurosurgical interventions. Intubation, ICU admissions, administration of mannitol.	Age Sex Mechanism of Injury ISS AIS	533 patients TBI and ICH 142 met the inclusion/exclusion criteria 47 underwent a routine repeat CT within 24 hours (violation of policy)- 0/47 neurosurgical, 1/47 had incidental finding on CT 95 no repeat routine CT within 24 hours 8/95 (non-violation group) had repeat CT >24 hours after admission- due to concern. 3/8 progression on CT	**Study Recruitment: High risk** Patients at GCS15 at 24 hours- low risk group selected out- difficult to extrapolated to all GCS13-15 patients. Does not compare outcomes in patient that adhered to and violated non-routine repeat CT head imaging. Potentially clinicians ordered routine repeat CT imaging on riskier patients. **Attrition: Low Risk**

	• GCS13-15 on arrival to ED • GCS 15 24 hours after attendance to ED • Did not receive a repeat CT head scan Excluded: • History of neurological or psychiatric disorder • Immediate neurosurgery • Previous TBI or neurosurgery • Spinal injury • Coagulopathy • Pregnancy • Transfers • Incomplete notes Patients that did undergo a repeat CT scan despite meeting the rest of inclusion/exclusion criteria formed a comparison group		ED revisits within 1 year for TBI related symptoms.		1 neurosurgical intervention 2/8 admitted to ICU due to deterioration- 1 intubated 3/95 patients returned with 1 year to the ED due to TBI symptoms- all underwent repeat CT. No admissions. Mean/median GCS=14.8 Mean/median age= 38 Percent anticoagulated=0	Potential for patients to have re-attended at other EDs and be missed **Prognostic factor measurement: Low risk** No risk model developed Factors abstracted from case notes **Outcome measures: low risk** Re-attendance at other EDs makes re-attendance a potentially biased outcome measure **Confounding Factors: Mod risk** Cohort includes patients with multiple injuries **Statistical techniques: Low risk** None presented Is a lower risk population due to selection for repeat CT imaging and return to GCS15 at 24 hours- possibly unable to include in any meta-analysis.
Ditty et al 2015 Alabama USA	University Alabama Level 1 trauma centre 2003-20013 Inclusion criteria: • 500 consecutive patients present on trauma registry • GCS13-15 • ICD9 diagnosis SAH and/or intra-parenchymal contusion- confirmed with radiology report and neurosurgical	Retrospective Cohort Study **Aim** Assess the clinical implications of SAH or intraparenchymal haemorrhage in mTBI	Neurological decline- altered mental state or focal neurological deficit. Inpatient seizure Delayed neurosurgical evacuation as inpatient. Inpatient mortality.	Admission GCS Anti-coagulation Anti-platelets Transfer Distances Sex Age Haemorrhage type	500 patients met inclusion criteria 411/500 isolated SAH 63/500 isolated ICH 26/500 both 463 GCS15 30 GCS14 8 GCS13 469/500 patients pre-hospital medication available (71/469 taking either anti-coagulants or anti-platelts) 156/500 transfers No patients had seizures.	**Study Recruitment: Mod risk** High proportion of transferred patients may represent higher or lower acuity patients than general population. Higher as being transferred to specialist centre, lower as survived /fit to transfer. No details about inclusion or completeness of trauma registry. **Attrition: Low Risk** Only inpatient measures **Prognostic factor measurement: Mod risk**

	consult note- if disagreement scan re-reviewed if not clear patient excluded Excluded: • Diagnosis extra or subdural hematoma • Penetrating injuries • Fatal extra-cranial injuries • CSF leak • Aneurysmal SAH • Delayed presentation				No patients had neurological decline. No patients underwent delayed neurosurgical intervention. No inpatient mortality	Incomplete information regarding medications. May be other inaccurate recording of factors. **Outcome measures: Mod risk** Only inpatient related outcome measures. Patients may have been discharged and deteriorated and presented to other hospitals. **Confounding Factors: Mod risk** Cohort includes patients with multiple injuries- only excluded if died from other injuries. **Statistical techniques: N|A** None presented Narrative synthesis- further evidence SAH low risk.
Pruitt et al 2016 Chicago USA	Level 1 Trauma Centre Chicago 2009-2013 Inclusion criteria: • Initial GCS13-15 • 16 and older • Traumatic intra-cranial bleed or skull fracture • Identified on electronic ED system using ICD 9 classification system • Admitted to ED observation unit All patients received a neurosurgical consultation	Retrospective cohort study **Aim** Assess if mTBI patients with intra-cranial haemorrhage can be managed to an ED observation unit	Clinical deterioration (defined as decrease in mental status, worsening neurologic exam or death) Neurosurgery during admission. Progression on CT.	Age Gender Method of arrival Whether transfer Comorbidities Anticoagulant use Mechanism of injury Initial GCS, Neurological examination Alcohol intoxication Initial platelet count INR Initial CT results Follow-up CT results, Neurosurgical recommendations Cranial CT data were collected from attending radiologist reports- type and	1185 GCS13-15 with CT detected injuries 814 admitted directly to hospital- poly-trauma, social reasons or as neurosurgeons felt high risk. 371 left under care of ED. Of these, 239/371 transferred ED obs unit. 132/371 discharged directly from the ED after a period of observation. **Admitted patients** Clinical deterioration 15/814 Worsening CT 27/814 Neurosurgery 33/814 Composite outcome 75/814 **ED obs unit** Clinical deterioration 0/239 Worsening CT 11/239 Neurosurgery 3/239 Composite outcome 14/239 Medical admission 4/239 Trauma/neurosurgery admit 8/239 **Follow up 190/239** Delayed Neurosurgery 0/239 Post traumatic seizure 3/239	**Study Recruitment: High risk** Neurosurgeons have admitted higher risk patients we can combine outcomes from both admitted and ED observed patients to give an unbiased estimate. **Attrition: Med Risk** Only a proportion of patients are followed up- does not describe the mechanism for this or how consistent follow up is e.g. did they all get repeat CT scans Prognostic factor measurement: Medium risk Dependent on CT scan reports and written documentation **Outcome measures: Mod risk** Clinical deterioration not well defined and very broad. **Confounding Factors: Low risk**

				size of detected injury	Concussive symptoms 16/239 **Discharged ED** **Follow up 111/132** Delayed Neurosurgery 1/132 Post traumatic seizure 2/132 Concussive symptoms 8/132 Figures from table- author has confirmed this is correct: *155 isolate SAH- 0 no clinical or radiological deterioration or cases of neurosurgery.* *161 SDH- 6 CT deterioration,* *3 planned neurosurgical outcomes.* *0 deteriorated clinically* *1 neurosurgery greater then 3 weeks later following outpatient assessment.* *30 contusion 5 worsening CT scans. Nil clinical deterioration or emergency neurosurgery.* *5 extradural- nil deterioration or neurosurgery* Of sample 1053 mean/median age=59 11% anticoagulated. Of sample 1185 mean median age=59 10% anticoagulated	Included patients with polytauma and significant comorbidities **Statistical techniques: High Risk** None presented but data presented in table and text do not match up Paper shows patients admitted to hospital by neurosurgeons have worse outcomes/more likely to require neurosurgery. Does show that in America some of this patient population discharged directly from ED. Consistent with the model used locally in Hull.
Deepika et al 2013 Bangalore India	Patients admitted tertiary neurosurgical centre 3 months Jan-March 2010. Patients identified on a TBI registry Inclusion criteria: • GCS 13-15head injury • Underwent CT scan • Either negative CT or Isolated traumatic subarachnoid • Matched comparison between patients -ve CT and SAH Excluded:	Retrospective cohort study **Aim** To assess whether GCS13-15 patients with traumatic subarachnoid haemorrhage have the same outcomes as mTBI patients with -VE CT scans	Prospective 1 year telephone assessment of : GOSE Rivermead post concussion questionnaire Rivermead Head injury follow up questionnaire	Age Sex Mechanism of injury- RTC Fall LOC Seizure Location of SAH Whether multiple bleeds Thickness greater or less than 5mm	34/1628 mTBI patients isolated traumatic subarachnoid haemorrhage 18/34 patients available for follow up at 1 year Good GOSE Rivermead scores comparable to 16 normal CT controls	**Study Recruitment: Low risk** Cohort identified in TBi registry which is part of normal practice. Is retrospective so limited by accuracy of medical notes. **Attrition: High Risk** Small sample- with large proportion lost to followup. **Prognostic factor measurement: Medium** risk Dependent on CT scan reports and written documentation **Outcome measures: High risk** 1 year too long **Confounding Factors: Medium risk** No control for other injuries or comorbidities

	• Does not state adults only but age range 15-67					**Statistical techniques: N/A** Too poor quality to include
Kreitzer et al 2014 Cincinnati USA	Level trauma center 2001-2010 Identified from cohort of patients undergone 2 CT within the ED within 24 hours Inclusion criteria: • GCS 14-15 and blunt head injury • Presented within 24 hours injury • Intra-cranial bleed first CT defined extradural, sundural, SAH, intra-cerebral and cerebral contusion • 2nd CT within 24 hours Excluded: • Incomplete notes • Pregnant • Intubated prior to ED evaluation • Abnormal observations • Penetrating injury • CT scans interpreted at different hospital • Coagulopathy either inherited or acquired • INR>1.4 (even if taking warfarin) • Platelets less than 50 • Any non-head injury mandating admission	Retrospective cohort study Standard practice repeat CT at least 6 hours after 1st CT if mTBI with ICH. If CT and patient stable discharge from ED. Aim: Assess outcomes for patients with mTBI and ICH	Death within 30 days Neurosurgical intervention within 2 weeks Return to the Ed within 7 days of discharge	CT head findings Age Race Sex Medical background	323/1011 patients that under-went 2 CT head within 24 hours in ED met the inclusion criteria After second CT 92/323 admitted 25/323 observed in ED and subsequently discharged 206/323 discharged 4 patients died (3 admitted 1 discharged) States death in discharged patient unlikely to be related to head injury had further fall. Also 1 other patient dies of septic shock. 3 neurosurgical interventions (all admitted) 28/206 discharged patients returned to ED within 1 week. None re-admitted and some planned- removal of sutures. Mean/median age= 42 Percent anticoagulated=0	**Study Recruitment: Mod risk** Identified through repeat CT imaging in ED- relies on all of cohort having repeat scans and patients deteriorate and not undergoing second scan being missed **Attrition:Low Risk** Followed up through social security system for deaths and the rest are inpatient outcome. Possibility of patients re-attending at other ED **Prognostic factor measurement: Medium** risk States that some CT are reported by radiology trainees overnight and then corrected by attending radiologists the next day- unable to quantify how much inaccuracy there is. Does state 32% of repeat scan normal **Outcome measures: low risk** Reasonable outcome measures **Confounding Factors: Low risk** Controls for comorbidities and other injuries **Statistical techniques: N/A**

	• Age less than 18					
Ding et al 2012 Neurosurgical Center China	Neurosurgical Centre China 2009-2010 Inclusion criteria: • All patients with TBI with evidence of intra-cranial haemorrhage- some data for GCS13-15 Excluded: • Immediate neurosurgery • Died within 3 days • Severe multiple injuries • Failed to undergo a repeat CT head	Appears to be a random control trial comparing outcomes in patients with traumatic intra-cranial haemorrhage assigned either to a routine repeat CT or CT only if deteriorates	GCS at discharge Surgical and medical interventions secondary to CT	CT scan results Initial GCS Mechanism of Injury Coagulation INR and platelets	32/89 patients in routine CT group GCS13-15 2/32 worse CT scans No patients had neurosurgery or altered medical management Mean/median age= 48	**Study Recruitment: High risk** Allocation to intervention and non-intervention arm not clearly explained- states via random number generator **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium** risk No re-reporting of CTS **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Low risk** Controls for other injuries **Statistical techniques: N/A**
Huynh et al 2006 USA	Level 1 trauma centre 2004-2005 Identified case note review Inclusion criteria: • mTBI • Blunt trauma to head • GCS 15 • Abnormal CT head Excluded: • Normal initial CT head • Length of admission less than 48 hours • Age less than 18	Retrospective cohort study **Aim** To assess whether neurosurgical review is necessary in GCS 15 patients with intra-cranial injuries	Changes on follow up CT- all patients had routine repeat CT Neurosurgical intervention	Demographics Mechanism of Injury ISS LOC Amnesia Associated injuries	56 patients met inclusion criteria 4/56 patients worse repeat CT Of these 4: 2/56 patients had fall in GCS to 14 from 15 1/56 given mannitol due to worse CT 1/56 loaded with phenytoin for seizures No consistent measure of deterioration 0/56 neurosurgical interventions 0/56 deaths Mean/median GCS=15 Mean/median age= 41	**Study Recruitment: Medium risk** Weaknesses of a retrospective case note review Higher risk group as admitted for at least 48 hours **Attrition: Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium** risk No re-reporting of CTS **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Low risk** No controls for other injuries

						Statistical techniques: N/A
Almenawer et al 2013 Ontario Canada	Neurosurgical centre Ontario, Canada 2006-2011 Identified from trauma database Inclusion criteria: • GCS13-15 • Blunt traumatic head injury • Age>17 • Intra-cranial injury CT head • Repeat CT scan Excluded: • No repeat CT scan • Previous caniotomy • Cranial pathology • Coagulopathy • Immediate Neurosurgery Patients divided into those underwent intervention due to clinical deterioration or due to repeat CT findings	Retrospective cohort study + meta-analysis to assess whether repeat CT imaging necessary in mTBI with intra-cranial haemorrhage	Intervention including: Mannitol or hypertonic saline Surgical intervention including ICP bolt or craniotomy Neurological changes: decrease GCS, cranial nerve change, vomiting and headache	Demographics GCS ISS	1121 patients with mTBI and ICH 445 met inclusion criteria 91/445 worse CT 21/445 patients neurosurgical outcomes (all preceded by clinical deterioration prior to repeat ct) 4/445 patients medical intervention 2/4 medical outcomes= treated with mannitol due solely worse CT other 2 treated due to clinical deterioration. Mean/median GCS=14.5 Mean/median age= 45 Percent anticoagulated=0	**Study Recruitment: High risk** Dependent on accuracy of trauma database Large proportion of mTBI patients with ICH did not meet inclusion criteria- selection out of higher risk patients that did not undergo repeat imaging **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium** risk No re-reporting of CTS **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Low risk** No control for poly trauma **Statistical techniques: N/A**
Sifri et al 2004 USA	Level Trauma Centre New jersey 1999-2001 Inclusion criteria: • GCS 14-15 • Blunt traumatic head injury • Age>15 • Intra-cranial injury CT head • Repeat CT Excluded:	Retrospective Cohort Study: To assess the value of routine repeat CT imaging in mTBI patients with intra-cranial haemorrhage	Worse CT Inpatient neurological deterioration- abnormal neurology- confusion, disorientation or drowsiness Inpatient neurosurgical interventions	CT results as abstracted from radiologist and neurosurgeons reports. Best ED GCS Demographics	243 patients with mTBI and ICH 18/243 excluded as no repeat CT- neurosurgeon ruled insignificant lesion 202/243 included as met the rest of inclusion criteria At 24 hours: 151/202 persistently normal or improving neurology 51/202 persistently abnormal or worsening neurological examination 50/202 worse CT	**Study Recruitment: Medium risk** Selection out of patients not undergoing repeat CT hea dimaging **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium** risk The definition of abnormal neurology is loose and not clear when it developed- not an admission criteria factor **Outcome measures: Medium risk**

	• History of brain injury • Coagulopathy including known bleeding disorder or taking warfarin • Immediate neurosurgical intervention including transfer to ICU				5/202 required neurosurgery- all had persistent or worsening neurology 1/202 died all in the persistently abnormal/ worsening neurology group No clear measure of deterioration Mean/median GCS=14.7 Mean/median age= 44 Percent anticoagulated=0	No outcome measures after discharge **Confounding Factors: Low risk** No control for poly-trauma and comorbidites **Statistical techniques: N/A**
Phelan et al 2014 Dallas USA	Level 1 Trauma Centre Dallas Texas 2010-2012 Patients identified on TBI data base Inclusion criteria: • Intracranial haemorrhage • TBI • Patients divided into SAH and non SAH bleed • All GCS but data for GCS13-15 patients presented Excluded: • Ages less than 18 • Pregnant • Prisoners	Retrospective Cohort Study Assess whether outcomes for mTBI with isolated traumatic subarachnoid differ for other kinds of intra-cranial bleeds	Worse repeat CT imaging if any Death Craniotomy	CT findings as reread by a study team member Age ISS HAS Emergency department GCS	77 patients GCS13-15 and traumatic SAH 27/77 scheduled repeat CT 3/27 worse CT 50/77-no routine repeat CT 4/50- unscheduled repeat CT 1/50- clinical deterioration and worse CT 4/77 worse CT 0 neurosurgical intervention	**Study Recruitment: Low risk** Dependent on accuracy of trauma registry **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: low** risk Does not really assess prognostic value of factors measured **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Low risk** No control for poly-trauma and comorbidites **Statistical techniques: N/A**
Homnick et al 2012 New Jersey USA	New Jersey Medical School Level 1 trauma centre 2002-2005 Inclusion criteria: • Age>17 • GCS>12 • TBI with positive initial CT-intracerebral	Retrospective Cohort Study Establish how long intra-cranial bleeds in mTBI continue to expand	Neurosurgical intervention Progression on CT-repeat CTs as discretion of neurosurgeon	Age Sec Pre-injury anti-coagulation Mechanism ISS Initial GCS	341 patients in study (85 mTBI patients with bleeds excluded as no F/U scan) 72/341 intubated in ED 105/341 progression on CT 13/341 death- 9 due to TBI 4 other causes 12/341 neurosurgical intervention Mean/median GCS=14.6 Mean/median age= 47	**Study Recruitment: Medium risk** Selection out of lower risk patients that did not have repeat CT imaging **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: low** risk Does not really assess prognostic value of factors measured

	bleed, contusion, subdural, extra-dural or SAH Excluded: • Penetrating trauma • Injury >24 hours previously • Previous neurosurgery • Non-traumatic mass on CT • Immediate neurosurgery				Percent anticoagulated=2	**Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for poly-trauma and comorbidites **Statistical techniques: N/A**
Nasir et al 2011 Karachi Pakistan	Specialist Centre Karachi Non-probability consecutive sampling Inclusion criteria: • GCS14-15 • All ages-15% sample children mean age 36 2 SD 18 • TBI with positive initial CT intra-cranial injury Excluded: • Clinical deterioration • Immediate neurosurgery • Isolated pneumocephalus All patients had a repeat CT within 72 hours	Retrospective Cross-sectional study **Aim:** Assess the utility of repeat CT scanning in mTBI patients with intra-cranial injuries without clinical or neurological deterioration	Worse CT	Age Gender Initial GCS Mechanism of injury CT findings	275 patients met inclusion criteria (note states 255 contusion haematoma) 17/275 worse CT No patients required neurosurgery Mean/median GCS=14.7 Mean/median age= 36 Percent anticoagulated=0	**Study Recruitment: Medium risk** Does not adequately define deterioration or over what period **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: low** risk Does not really assess prognostic value of factors measured **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for poly-trauma and comorbidites **Statistical techniques: N/A** **Overall** Includes kids and quite a different population than North America and Europe.
Boris et 2013 Israel	Israel Level 2 trauma centre Sates 2007-2011 Inclusion criteria: • GCS14-15	Retrospective Cohort Study Assess whether repeat CT imaging in GCS14-15 mTBI	Increased size of bleed second CT Clinical deterioration-decrease in GCS	Age Sex Initial and follow-up GCS CT findings	68 patients 4 patients transferred to neurosurgery (2 routine) 8/68 patients worse CT 12/68 mild deterioration	**Study Recruitment: Medium risk** Identified on trauma data base with patients with incomplete data excluded. Does not present number of these patients. Also excludes patients transferred immediately.

	• TBI with positive initial CT intra-cranial injury including subdural, extra-dural, subarachnoid and intra-cerebral bleeds • Only data for adults presented Excluded: • Patients with incomplete data • Transferred to neurosurgery immediately • No repeat CT All patients had a repeat CT within 12 hours	with intracranial injury justified	New motor or sensory symptoms Severe headache or vomiting		28 patients intra-parenchymal bleed 1/28 worse CT 3/28 neurological deterioration 1/28 transferred to neurosurgery (not patient with worse CT) 7 patients extra-dural 1/7 worse CT 0/7 neurological change 1/7 transferred to neurosurgery 20 patients sub-durals 3/20 worse CT 4/20 neurological deterioration 1/20 neurosurgery 13 patietns SAH 3/13 increase in size bleed 5/13 neurological deterioration 1/13 transferred to neurosurgery Mean/median GCS=14.8 Mean/median age= 56	Likely to be lower risk smaple than population of interest. **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: low** risk Does not really assess prognostic value of factors measured **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for poly-trauma and comorbidites **Statistical techniques: N/A**
Brown et al 2007 Los Angeles USA	Los Angeles Level 1 trauma center 2003-2004 Inclusion criteria: • All patients with blunt head trauma and intra-cranial bleed initial CT. Presents data for GCS13-15 Excluded: • Immediate neurosurgery • Died within 24 hours • Does not state just adults but seems only for adults	Prospective Cohort Study **Aim** To identify patients with head injuries that benefit from routine repeat CT imaging	Need for neurological intervention- either medical or surgical (medical= sedatives, mannitol or hyperventilation and surgical= ICP monitor and craniotomy) Mortality	Age Gender Mechanism of Injury ISS Admission GCS Results of CT-interpreted by attending radiologist	354 patients all GCS scores with intra-cranial bleed 37 direct to craniotomy 43 dies within 24 hours 274= study population 142/274= mTBI GCS13-15 15/142 had clinical deterioration 27/142 had worse CT scans (only 72/142 had repeat imaging) 5/142 had medical or neurosurgical intervention 3/142 died Mean/median GCS=14 Mean/median age= 43	**Study Recruitment: Mod risk** Removal of patients that died within 24 hours may lead to this sample being a lower risk group than population of interest **Attrition: Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: low** risk Does not really assess prognostic value of factors measured **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for poly-trauma and comorbidities- **Statistical techniques: N/A**

	(mean age 44 +/- 19)					
Thomas et al 2010 Tennesse USA	Tennesse Level 1 trauma centre 50 months from Jan 2001 Inclusion criteria: • All patients with blunt head trauma and evidence TBI on initial CT. Presents data for GCS13-15 • Age 18+ Excluded: • Penetrating mechanism • Immediate neurosurgery • Interventions for unclear indications • Died before second CT All patients repeat CT at 6-8 hours after admission	Retrospective Cohort Study To assess whether scheduled repeat CT head imaging is indicated in TBI	Neurosurgical interventions- craniotomy or ICP monitor Medical interventions- mannitol/hypertonic saline Neurological change-reduced GCS, pupillary change, increased ICP or loss of brain stem reflexes	Initial GCS ISS Race Age Gender Mechanism of injury History of vascular disease Anticoagulant use Antiplatelet use PT, aPPT, INR CT findings	457/836 in included sample population GCS13-15 14/457= neurosurgical intervention (craniotomy or ICP bolt) 3/457 medical management 5/14 neurosurgical interventions- based on repeat CT 3/14 medical interventions based on repeat CT Mean/median age= 42	**Study Recruitment: Mod risk** Dependent on case note review. Patient with "unclear" indications for interventions removed. **Attrition: Low Risk** Only inpatient outcome measures **Prognostic factor measurement: Mod risk** Does not explain how CT scans reported **Outcome measures: Mod risk** No F/U after discharge **Confounding Factors: Medium risk** No control for poly-trauma **Statistical techniques: N/A** None done
Klein et al 2010 Israel	3 regional trauma centres in Israel. None had access to neurosurgery on site. Identified ICD9 codes on national trauma registry. Inclusion criteria: • GCS13-15 • ICD9 code for intra-cranial bleed. One hospital transferred all patients to neurosurgical centre. Other 2 hospitals transferred selected patients.	Retrospective Cohort Study **Aim:** Assess the outcome of low risk patients with ICB managed in district hospitals without neurosurgical services	Mortality Neurosurgical intervention Neurological status at discharge	Age AIS ISS	323 patients all 3 hospital intra-cranial bleed and GCS13-15 27/323 required neuro-rehab 2/323 died 35/323 neurosurgery 77/323 not transferred- 0/77 died 0/77 neurosurgery 2/77 delayed transfer Non-transfer on basis of: Single bleed </= 5mm or contusion <1cm and no-coagulopathy Mean/median age= 39	**Study Recruitment: Low risk** Dependent on completeness of trauma registry **Attrition: Low Risk** Only inpatient outcome measures **Prognostic factor measurement: Mod risk** Does not explain how CT scans reported **Outcome measures: Mod risk** No F/U after discharge **Confounding Factors: Medium risk** No control for poly-trauma or comorbidities **Statistical techniques: N/A**

						None done
Sifri et al 2011 USA	Level 1 Trauma Centre New jersey 2002-2006 Inclusion criteria: • Initial GCS 13-15 • Blunt traumatic head injury • Age 18+ • Intra-cranial injury CT head-ICB or skull fracture • Repeat CT • Abnormal neurological examination at time of repeat CT Excluded: • Immediate or planned neurosurgical intervention • Normal neurology at time of repeat CT- normal neurology defined as GCS15, orientation to place, person or time, normal neurological exam, no symptoms from head injury- headache, vomiting, dizziness, lethargy • Coagulopathy including known bleeding disorder or taking warfarin • Pregnancy • Spinal Cord Injury	Retrospective Cohort Study **Aim:** To assess proportion of patients that have worse CT scans and neurosurgical interventions that have abnormal neurology when they have a repeat CT.	Progression of lesion on CT Surgical intervention- includes intubation Medical intervention GOSE at discharge	Demographics Acute deterioration in neurological Exam Persistently Abnormal Neurological exam Unknown whether change as intubated	107 patients met inclusion criteria 63/107 worse CT=59% 7/107 neurosurgical group 21/107 deterioration 18/107 unable to assess neurology as intubated. 6 died Mean/median GCS=14.4 Mean/median age= 48 Percent anticoagulated=0	**Study Recruitment: High risk** High risk subgroup that have abnormal neurology at time of repeat CT imaging. **Attrition: Low Risk** Only inpatient outcome measures **Prognostic factor measurement: Mod risk** Difficult to assess deterioration in a retrospective study. **Outcome measures: Mod risk** No F/U after discharge **Confounding Factors: Low risk** Some control for comorbidities. **Statistical techniques: N/A** None done

	• Prior brain surgery • Acquired or congenital cerebral pathology or existing neurological or psychiatric disorder					
Beynon et al 2015 Germany	Heidelberg University Hospital Germany 2013-2014 Inclusion criteria: • Initial GCS 13-15 • Traumatic Intra-cranial bleed CT head	Retrospective Cohort Study **Aim:** Compare outcomes in patients on different types of anti-coagulants	Repeat CT imaging Progression on CT Neurosurgery Death Mean GCS at discharge	Patients divided into those on no anticoagulants, Aspirin, Warfarin and DOACS. gender, trauma mechanism, comorbidities, CT findings, repeated CT imaging, age, GCS scores, laboratory values	70 patients met inclusion criteria 37 no anticoagulation 27 anti-platelets 5 warfarin 6 DOACS (rivaroxaban) 1 patient dabigatran 25% neurosurgery (18 patients) 43/70 repeat CT imaging- 2 deaths both on rivaroxaban Mean/median GCS=14.5 Mean/median age= 67 Percent anticoagulated=16	**Study Recruitment: Low risk** Although high rates of anti-coagulation. **Attrition: Low Risk** Only inpatient outcome measures **Prognostic factor measurement: Low risk** **May be miss-classified in medical notes** **Outcome measures: Mod risk** No F/U after discharge **Confounding Factors: Low risk** No control for comorbidities. **Statistical techniques: N/A** None done

Appendix 23: Data Extracted from Included Studies

Studies with univariate or multivariate risk factors N=21 (also included in pooled estimates outcome prevalence)

Reference	Population	Study Design	Outcome Measures	Prognostic factors assessed	Results	Quality Appraisal
Nishijima et al 2014 Sacramento USA	Single-site: Level 1 trauma centre 2009 – 2013 Inclusion Criteria: • Age ≥ 18 years • Consecutive patients • Initial ED GCS 13-15 • CT +ve ICH-SAH, SDH, EDH, intra-ventricular, intra-parachymal bleed/contusion, diffuse axonal injury Exclusions: • Patients with DNACPR • Patients pre-injury anti-coagulant use	Prospective cohort study **Aim:** Derive a clinical decision instrument for patients with mild ICH low risk requiring critical care intervention. **Statistical Method:** Derived clinical decision instrument with binary recursive partitioning (misclassification cost 20:1). Performance of instrument compared to clinical impression.	critical care invention within 48 hours of arrival ED: • Intubation • Neurosurgery including ICP monitoring/ giving mannitol/hypertonic saline • Transfusion RBC/FFP • Vasopressor /ionotrope use • Cardiac arrest/arrhythmia (HR<40, HR>120) • Interventional angiography	Age ≥ 65years Sex Dangerous mechanism (any non-fall from standing mechanism) Pre-injury antiplatelet use (aspirin or clopidogrel) High risk co-morbidity ED Vital signs GCS <15 at admission BP<90 at any point ED Sats <95% at any point ED Lab results: Platelet count INR Haematocrit Initial CT: Midline shift/absence cisterns Depressed skull fracture	600 patients 71% male 0.5% died + 6.5% neurosurgery + 8.3% intubated 68% GCS 15 93% admitted ICU 19.3% had crit care intervention 9.2% transfusion 8.3% intubation 6.5% Neurosurgical 4 predictors need for crit care intervention: (Recursive partitioning) GCS<15 (RR 2.95; 95% CI 2.21-4.12) ≥ 65years (RR 1.46; 95% CI 1.05-2.03) CT midline shift/absence cisterns (RR 4.11; 95% CI 3.08-5.48) Non-isolated head injury (RR 2.74; 95% CI 1.99-3.78) Sensitivity of decision rule to predict intubation/neurosurgery within 48 hours of admission ED. 98.6% specificity 36.6% To any crit care inteverntion Sensitivity 98.3% 95% C.I. (93.9-99.5%) Specificity 39.7% 95% C.I. (35.4-44.1%) Positive predictive value 28.1% 95% C.I. (23.9-32.6%) Negative predictive value 99% 95% C.I. (96.3-99.7%) Clinician impression: Do you think patient needs ICU? Sensitivity 90.1% 95% C.I. (83.1-94.4%) Specificity 49.2% 95% C.I. (44.7-53.8%) Clinical impression deterioration in 48 hours? Sensitivity 91% 95% C.I. (84.2-95.0%) Specificity 39.5% 95% C.I. (35.1-44.1%) Presence of swelling or shift on initial cranial CT RR (95% CI) 4.11 (3.08-5.48)	**Study Recruitment: Mod risk bias** Missed 20% eligible patients- not completely clear individuals in cohort identified. Otherwise clear inclusion and exclusion criteria. **Attrition: Low risk** Follow up only 48 hours so low risk of attrition bias. **Prognostic factor measurement: Low risk** Standardised and objective prognostic factor measurement. Collected all patients. **Outcome measures: Low risk** Recorded in uniform way for all patients. Only 48 hours. **Confounding Factors: Mod Risk** Additional severe injury may be related to prognostic factors and outcome measures. Not accounted for in in analysis. **Statistical techniques: low risk** Good presentation of methods **Overall summary** Risk factors identified by case note review/d/w treating physicans where not clear. Radiology attending written report used for CT findings. No independent quality verification- could introduce bias.

				Non-isolated head injury AIS score 3 or more additional injury	Admission GCS score less than 15 RR (95% CI) 2.95 (2.12-4.12) Non-isolated head injury RR (95% CI) 2.74 (1.99-3.78) Hypotension prior to admission RR (95% CI) 2.70 (1.61-4.54) Presence of depressed skull fracture RR (95% CI) 2.44 (1.46-4.08) Presence of any high-risk co-morbidity 1.58 (1.07-2.33) RR (95% CI) Pre-injury antiplatelet use 1.54 (1.04-2.30) RR (95% CI) Hypoxia prior to admission 1.52 (1.03-2.24) Age 65 years or older RR (95% CI) 1.46 (1.05-2.03) Non-fall from standing mechanism of injury RR (95% CI) 1.12 (0.80-1.57) Mean/median GCS=14.6 Mean/median age= 52 Percent anticoagulated=0	CT end point also missed spectrum of possible findings. Outcomes out 48 hours too short, also crit care intervention definition very broad- e.g. transfusion. No blinding to exposure/outcomes. Overall good internal validity of study. But issues with generalising results: Exclusion of anti-coagulated patients. Short outcome measurement 48 hours. Outcome measures of critical care intervention quite soft- including transfusion of blood products. No external validation of results.
Sweeney et al 2015 USA	Identified on national trauma data base 2007-2012 Inclusion criteria: • Age ≥ 18 years • ED inital GCS 14-15 • ICD 9 code intra-cranial injury= cerebral contusion, SAH, SDH, EDH, multiple TBI • Admitted to hospital Exclusions: • ICD9 diagnoses skull fractures • Penetrating mechanism of injury	Retrospective Cohort study Hypothesis that injury type associated with deterioration in isolated TBI. Multiple logistic regression used to assess risk of outcomes. Mixed effects model to explore potential differences between hospitals.	Neurosurgical Intervention: Defined as operative procedure, or placement of an ICP monitor. Identified by ICD9 coding.	ISS (measure of head injury severity due to exclusion criteria). Coagulopathy (pooled measure of Vit K deficiency, haemophilia, thrombocytopaenia, chronic anti-coagulant therapy) Chronic aspirin use not included. Type of intra-cranial injury as per ICD 9 code. ED vital signs Age	50496 patients met criteria 4474/50496 neurosurg 58% admitted to ICU EDH-N=901 18% Neurosurg SDH-N=18784 16% Neurosurg Mixed N=11984 8% Neurosurg SAH N=13191 1.5% Neurosurg Contusion N=5636 Data set split into 2/3 training set and 1/3 test set. Adjusted odds ratios for neurosurgical procedures. Multiple logistic regression run on 2/3 training set (n = 33,327) Age (years) OR=1.002 (95% CI0.999 – 1.01) P=0.18 Anticoagulation Disorder OR=0.853 (95% CI 0.66 – 1.09) P=0.21 ED GCS OR=0.894 (95% CI 0.781 – 1.03) P=0.11 ED Systolic Blood Pressure OR=1.004 (95% CI 1.002 – 1.01) P<0.001 ED Pulse OR=0.99 (95% CI0.986 – 0.993) P<0.0001 ED Respiratory Rate OR=0.962 (95% CI0.944 – 0.98) P<0.0001 ISS 7-11 OR=2.35 (95% CI 1.44 – 4.09) P<0.01	**Study Recruitment: High risk bias** Eligible patients recruited through a relatively new national trauma data base by ICD9 coding. Potential selection bias as to which hospitals upload data. Also uncertain how accurate coding is. Excluded patients with incomplete data, they may be systemically different. **Attrition: Low risk** As a trauma registry represents routine information that should be consistently on all eligible patients. **Prognostic factor measurement: Mod risk** Grouping of coagulopathy problematic, different likely risk of warfarin versus ITP for example. CT findings watered down to code for injury, misses important information.

	• AIS score>1 any other body region • Data missing ED vital signs				ISS 12-18 OR=3.37 (95% CI 2.06 – 5.86) P<0.0001 ISS 19-27 OR=18.9 (95% CI 11.6 – 33) P<0.0001 ISS >27 OR=7.01 (95% CI 3.79 – 13.4) P<0.0001 Injury Category (vs. Contusion) Isolated SAH OR=0.95 (95% CI 0.64 – 1.41) p=0.79 Isolated SDH OR=4.9 (95% CI 3.61 – 6.84) P<0.0001 Isolated EDH OR=6.42 (95% CI 4.15 – 9.97) P<0.0001 Multiple Injury Types OR=2.34 (95% CI 1.7 – 3.29) P<0.0001 After adjustment injury severity, age, coagulopathy and ED vital signs: injury pattern significantly associated need for neurosurgery: OR EDH versus contusion 6.4(95% CI 4.1-9.9). Age no association. ED vital signs also predictive. In test AUC ROC curve= 0.81 in test set Hosmer-Lemeshow P = 0.8 in test set 38% expected and observed rate of neurosurgery highest risk decile. O.5 % in lowest risk decile. Mean/median age= 61 Percent anticoagulated=5	**Outcome measures: Moderate risk** Need for neurosurgery only as recorded on trauma data bank, possibly unreliable. Misses other important adverse outcome e.g. death and intubation. Does not include time scale from presentation or what happens to patients who are discharged and re-attend with adverse outcome. Follow up not clear **Confounding Factors: Low risk** Excluded other injuries and made adjustments in logistic regression model. No attempt to control for co-morbidities. **Statistical techniques: low risk** Good presentation of methods Finds that injury type significantly associated with need for neurosurgery -provides candidate factors. There are methodological problems with paper.
Joseph et al 2015 USA Is MTBI defined by GCS: is it really mild?	Level 1 trauma center Arizona Retrospective case note review 2009-2012 Inclusion criteria: • Initial GCS13-15 • Aged 18+ • Initial scan +VE ICH/skull fracture and routine repeat scan still showed injury	Retrospective Chart Review **Aim** Identify factors that predict progression on CT imaging and neurosurgical intervention in GCS13-15 patients . **Method** All patients underwent routine repeat CT imaging within 6	Progression on repeat CT Neurosurgical intervention= craniotomy or craniectomy as inpatient	Age Gender Race Ethnicity Mechanism of injury GCS BP HR FBC Serum lactate Base deficit AIS ISS CT findings- reviewed by an investigator that was part of the team- classified size	876 patients met inclusion criteria **115 (13.1%)=progression on CT** Univariate predictors: Age 65+ p=0.07 OR1.5(0.9-2.5) Male p=0.8 OR1.1 (0.6-1.7) Intoxication p=0.9 OR1.3 (0.3-4.7) Mechanism of injury p=0.5 OR 1.1 (0.3-2.8) HR>100 P=0.7 OR1.1 (0.6-1.8) BP<90 p=0.35 OR 1.3 (0.45-1.9) LOC p=0.2 OR1.2 (0.6-2) Displaced skull fractue P=0.02 OR 1.9 (1.1-3.3) SDH >10mm p=0.004 OR3.4 (1.5-8) EDH >10mm p=0.01 OR3.8 (1.2-7.6) Hgb<10 P=0.4 OR 1.5 (0.76-3.1) Platelets less than 100000 p=0.04 OR 1.5 (1.1-3.9) Lactate =/<2.5 p=0.18 OR2.6 (1.2-5.5) (?!)	**Study Recruitment: Mod risk** Retrospective identification of case notes- depends on accuracy of case notes Excludes patients on anti-coagulatants and anti-platelts **Attrition: low risk** Outcomes only as inpatients **Prognostic factor measurement: Low risk** Relies on accuracy of medical notes. Re-examines CT images **Outcome measures: Mod risk**

	• Isolated TBI as defined head AIS greater/equal 3 and AIS <3 other body regions Excluded: • On Anti-platelets • On Anti-coagulants • Transfers • Needed immediate neurosurgery.	hours of initial CT imaging. Univariate analysis to identify risk factors for progression on CT or neurosurgery. P=/<0.2 included multivariate analysis		of lesion and whether progression on CT	Base deficit>4 p=0.02 OR 3.1 (1.2-7.6) Multi-variate Analysis: Age 65+ P=1.4 OR 1.4(0.7-2.7) LOC P=0.8 OR1.1 (0.5-2) Displaced skull fracture P=0.08 OR 2.3 (0.9-3.5) SDH>10mm P=.0.007 OR 4.8 (1.9-9.6) EDH>10mm P=0.001 P=7.9 (2.4-12.6) Platelets less than 100000 p=0.1 OR 1.3 (0.9-3.6) Lactate =/<2.5 p=0.2 OR 2.1 (0.89-2.5) Base deficit>4 p=0.01 OR 2.8 (1.6-4.1) **47 (5.4%)= neurosurgery** Univariate predictors: Age 65+ p=0.3 OR 1.08 (0.8-1.3) Male P=0.19 OR 1.2 (0.8-1.3) Intoxication P=0.3 OR1.8 (0.9-3.4) BP<90 p=0.35 OR 1.3 (0.45-1.9) Mechanism P=0.34 OR1.2 (0.4-1.8) LOC p=0.19 OR1.4 (0.7-3.2) HR>100 P=0.26 OR 1.5 (0.9-2.8) Displaced skull fractue P=0.01 OR 16 (7.6-19.6) SDH >10mm p=0.001 OR3.9 (2.4-5.1) EDH >10mm p=0.03 OR4.8 (2.9-5.6) Hgb<10 p=0.51 OR 1.2 (0.6-2.5) Platelets less than 100000 p=0.31 OR 2.5 (1.15-5.1) Lactate =/<2.5 p=0.12 OR3.6 (0.7-6.5) Base deficit>4 p=0.01 OR 23 (1.6-31) Multi-variate Analysis: Male p=0.1 OR 1.6 (0.8-2.1) LOC P=0.3 OR1.2 (0.5-1.9) Displaced skull fracture P<0.001 OR 10 (6.7-12) SDH>10mm P<0.001 OR 3.4 2.1-4.46) EDH>10mm P=0.006 P=3.5 (1.4-5.5) Platelets less than 100000 p=0.09 OR 1.3 (0.98-4.8) Lactate =/<2.5 p=0.21 OR1.9 (0.62-3.1) Base deficit>4 p=0.001 OR 21 (1.6-27) Mean/median GCS=14.3 Mean/median age= 54 Percent anticoagulated=0	Only measures as inpatient. Potential for discharge and deterioration. **Confounding Factors: low risk** Possibility of confounding due to other comorbidities- does not adjust for this, **Statistical techniques: Mod risk** Some of the results appear to be reported wrong. E.g. Lactate **Overall** Presents useable data for analysis **Note base deficit found to be highly prognostic- only study to assess this.**

Borczuk et al 2013 USA	Level 1 trauma centre Boston Case note review 2009-2010 patients identified through ED electronic coding ICD9 coding for intra-cranial haemorrhage. Inclusion criteria • GCS 13-15 • Age 15 or older • CT positive traumatic intra-cranial haemorrhage Excluded: • Isolated Skull fractures	Described as a cross sectional study Seems more like a retrospective cohort study Aims Develop a set of criteria to identify patients who are at low risk for deterioration and thus may not require neurosurgical evaluation **Method** Univariate analysis to predict composite outcome of deterioration 3 factor multivariate model derived from univariate analysis	Deterioration whilst in hospital including: Decrease in GCS Worsening neurological examination Worsening CT result on repeat CT Neurosurgery Death Composite outcome All outcomes whilst in hospital- no discharge outcomes	Data extracted from case notes by 2 ED researchers. Not blinded to the hypothesis Age Method of arrival History of HTN Anti-coagulation Mechanism Initial GCS Neurological examination Alcohol Intoxication Initial platelet count INR Initial CT result F/U CT result CT categorised by attending radiologist type, location and size of bleed/contusion. Presence of midline shift	404/863 TBI patients met inclusion criteria (46.8% patients with traumatic bleeds). 11.8%(48) deteriorated 5.9% neurosurgical Deterioration stratified by injury: 24/136 isolated SDH 0/1 isolated EDH 1/75 isolated SAH 2/31 contusions 22/161 mixed lesions Univariate predictors of deterioration: Age 65+ OR 0.93 95%CI 0.5-1.69 Sex OR 0.77 95%CI 0.41-1.41 Fall OR 0.57 95%CI 0.29-1.09 Assault OR 1.07 95% CI 0.45-2.51 RTC OR 0.51 95%CI 0.12-2.21 Pedestrian Struck OR1.12 95% CI0.32-3.92 Bicycle Struck OR 1.51 95%CI 0.42-5.44 HTN OR0.94 95%C.I. 0.51-1.73 Aspirin OR 0.79 95% CI0.41-1.51 Warfarin OR0.87 95% CI 0.33-2.32 Clopidogrel OR1.25 95% CI 0.27-5.75 GCS<15 OR 2.12 95% CI 1.01-4.43 CT findings Any lesions SDH OR 2.64 95% CI 1.20-5.83 EDH OR 2.4 95% CI 0.91-6.31 SAH OR 0.42 95% CI 0.22-0.81 Contusion OR 0.79 95% 0.39-1.62 Isolated lesions SDH OR 1.62 95% CI 0.88-2.96 EDH OR only 1 patient SAH OR 0.078 95% CI 0.01-0.59 Contusion OR 0.46 95% 0.11-1.96 Multiple logistic regression with 3 variables GCS=15, presence SDH and presence isolated SAH: All remained significant predictors of deterioration. Sensitivity 97.9% and specificity 20.8% Negative predictive value 99.6%	**Study Recruitment: low risk** Dependent on how good electronic coding is and case note review was. **Attrition: Low risk** Follow up only for period in hospital **Prognostic factor measurement: Low risk** Written CT reports from attending radiologist used for data extraction. No verification of accuracy or consistency. **Outcome measures: Mod risk** No F/U following discharge- missed delayed outcomes, could have looked for re-attendance. GCS and neurological examination also potentially subjective. **Confounding Factors: Mod risk** No attempt to control or exclude polytrauma patients or patients with multiple comorbidities **Statistical techniques: Mod risk** Good univariate analysis Small number prevented large enough multi-variate model

					Positive predictive value 38.8% Mean/median GCS=14.8 Mean/median age= 60 Percent anticoagulated=10	
Washington et al 2012 USA	Level I trauma center Washington Retrospective case note 2-year period (January 2007-December 2008) Inclusion criteria: • Admission GCS score ≥ 13 • Isolated head injury with no other injury requiring ICU admission • Initial head CT scan positive for any type of ICH • Initial non-operative. management plan Excluded: • Patients requiring immediate neurosurgery surgery	Retrospective Cohort Study **Aim** To determine if there exists a sub-population of mild TBI patients with an abnormal head CT scan that requires neither repeat brain imaging nor admission to an ICU Standard of care is to admit these patients to ICU and routinely re-CT **Methods:** Univariate and multivariate analysis for outcomes of interest	Neurological or medical decline. The need for neurosurgical intervention. The GOS score. Neurological decline was defined remaining in the ICU or transfer back to an ICU or intervention as a result of a decline in mental status or the development of a neurological deficit. Medical decline was defined as an increase in monitoring or intervention due to cardiac, pulmonary, or renal decline. Outcome measures during admission and at discharge.	Age Sex, Injury mechanism Initial GCS score Duration of hospital stay. Aspirin/Clopidogrel/ Warfarin use Ttransfusion of blood products Intubation CT scans classified into Marshall and Rotterdam Criteria-blinded assessment by author	321 patients met the inclusion criteria Neurological decline 1% 4 Surgical intervention 1% Medical decline 6% 18 Cardiac event 7% Respiratory event 4% Seizure event 2% CT progression 6% GOS score at discharge: 1 1% 2 0% 3 4% 4 10% 5 85% Age + transfusion predictors of a medical decline ($p < 0.01$). Odds ratio of having a medical decline after undergoing a blood product transfusion was 12.55 (95% CI 4.3–36.7). Cardiac and respiratory events the odds ratios were 5.6 (95% CI 2.4–13.1) and 8.8 (95% CI 2.6–30.4). Significantly higher mortality transfused group as compared with the non-transfused group (6% vs 0%, respectively, $p < 0.0001$, Fisher exact test). Higher rate of brain injury progression in the transfused patients (13% vs 5%, $p = 0.04$). Predictors of bleed progression univariate analysis: ICH vol >10 ml OR 20.13 95% CI (5.67–71.44) subfrontal/temporal contusion OR 5.73 95% C.I.(2.20–14.89) age ≥65 yrs OR4.00 C.I>(1.40–11.42) antiplatelet &/or Coumadin therapy OR 2.94 C.I. (1.12–7.71) Unclear which other factors assessed.	**Study Recruitment: low risk** Through case note review-potential for patients without notes to be missed **Attrition: low risk** Follow up only for period in hospital **Prognostic factor measurement: Low risk** Case note extraction- potentially incomplete CT scans re-reported. Uses Marshall classification **Outcome measures: Mod risk** Outcome measures only during hospital admission. No measure of re-attendance or community outcome F/U The outcome measures of neurological and medical decline are subjective. **Confounding Factors: Medium risk** No control for other injuries and comorbidities **Statistical techniques: High risk** Selective reporting of significant risk factors and does not present full analysis. No analysis to predict neurosurgical outcomes. Potentially can re-analyse the data from what is presented

					States: "multivariate analysis was performed, only an ICH volume > 10 ml was independently associated with the risk of hemorrhagic progression. Patients with a hemorrhage volume > 10 ml were 20.13 times more likely to have progression on head CT. Mean/median GCS=14.8 Mean/median age= 57	
Choudhry et al 2013 USA Identified Search Strategy	Level 1 trauma center New Jersey Retrospective cohort patients in trauma data base 2002-2006 Inclusion criteria: • GCS>12 • Initial scan +VE ICH Excluded: • Discharged • Pregnancy • Needed immediate neurosurgery • Spinal cord injury • Brain surgery or existing cerebral pathology • Chronic neurological/psychiatric disorder e.g. dementia • Incomplete medical records • Use of sedating drugs Age range 18-90 in results	Retrospective cohort study using trauma data base. **Objective:** To identify the cause, temporal course and outcomes of patients who deteriorate neurologically after presenting with MHI and ICH **Methods** Presents univariate and multivariate risk of death	Outcome measures: Delayed neurological deterioration defined as: GCS drop 2 or more points for more than 1 hours New focal neurological deficit Death Neurosurgical intervention Worse CT if performed- worsening in Marshall criteria or significant expansion in volume- neuroradiologist GOS outcome at 6 months	Collected data: Age, Sex, Ethnicity, Mechanism of injury, GCS, AIS, Coagulopathy	908 patients MHI and ICH 151 not included due to incomplete notes or meeting exclusion criteria 757= final cohort 31/757= delayed deterioration at inpatient. 4.1% (21 due to progression ICH, 10 due to medical causes) 7/757deaths 21/757 patients worse CT scans Univariate analysis outcome death Age>/=60 P=0.001 Coagulopathy P=0.02 Increase Marshall classification repeat CT P=0.001 Decline in consecutive GCS scores more than 6 P=0.02 Deterioration within 9 hours P=0.04 H-AIS>3 P=0.32 ISS>20 P=0.38 Initial GCS<15 P=0.40 Initial Marshall classification >II P=0.41 Age>60 predicted deterioration due to expansion of bleed and death in stepwise logistic regression (p<0.01) Mean/median age= 49	**Study Recruitment: Mod risk** Retrospective identification of patients on trauma database. Relies on patients being correctly recorded on this. Patients with incomplete notes excluded- may be systematically different. **Attrition: low risk** Reports no loss to F/U at 6 months routine clinic- may form part of group of patients excluded due to incomplete notes **Prognostic factor measurement: Low risk** Relies on accuracy of medical notes **Outcome measures: Mod risk** Outcome measure of delayed deterioration- relies on adequate checks on patients and neurological examinations in a consistent way. Assumes this is baseline level of care- likely to vary dependent on where the patients were admitted (e.g. ICU versus normal hospital bed) **Confounding Factors: low risk** Doesn't explicitly say for patients with only a head injury, if does include other injuries high risk for confounding. Also no adjust for comorbidities **Statistical techniques: High risk**

						Univariate outcomes for mortality presented only as P values. Performed multivariate stepwise regression- for mortality reports only one result without confidence intervals. **Overall** Compares patients with medical and neurosurgical deterioration and that died and didn't die with worsening CT scans. Much more pertinent to compare patients that deteriorated and didn't deteriorate.
Kim et al 2014 South Korea	University hospital Seoul South Korea Case note review from Jan 2002-Dec 2012 Inclusion criteria: • All patients with acute traumatic subdural bleeds Excluded: • Neurosurgery within 24 hours of admission • GCS<13 on admission • Patients with vascular abnormalities • Subdural localised to the falx/ tentorium cerebelli • Bilateral subdurals	Retrospective chart review **Aim:** To determine risk factors with delayed subdural enlargement leading to surgery in patients with acute subdurals	Delayed surgical evacuation of subdural haematoma	Age Gender Cause of trauma Presence of other CT findings GCS Neurological deficit Comorbidities History of antiplatelets Anticoagulation therapy INR Platelet count	98 patients included 51/98 progression on CT either at 1 week , 2 weeks or 3-10 weeks. 34/98 delayed surgical evacuation up to 10 weeks following trauma Univariate comparison between conservative and delayed neurosurgical group: Mean age P=0.375 Male, P=0.950 Glasgow Coma Scale P= 0.647 Hypertension P= 0.883 Diabetes P= 0.785 Smoking P=0.107 Alcohol abuse P=0.840 Use of anticoagulant P= 1.000 Use of antiplatelet agent P= 0.546 Thrombocytopenia (<50,000) P= 1.000 Prolonged prothrombin time (INR> 1.4) P=0.656 Cause of head trauma P0.651: Fall from standing Motor vehicle accident Fall from a height Assault Bicycle accident Mean SDH maximal thickness (mm, range) P<0.001* Mean SDH volume (ml, range) <0.001* Mean midline shift (mm) P<0.001*	**Study Recruitment: Low risk** Retrospective case note review- depends on information being recorded correctly. **Attrition: low risk** All patients appeared to have been followed up appropriately **Prognostic factor measurement: Low risk** Appears CTs have been reviewed and volume measurements conducted by member of study team **Outcome measures: Low risk** All patients followed up until clinic. No reports of deaths. **Confounding Factors: Low risk** None obvious-exclude patients with other injuries **Statistical techniques: Low risk** Well presented **Overall**

	• Aged less than 15 • Other significant injuries • Patients refusing surgery				Presence of cerebral contusion P= 0.003* Presence of SAH, P=0.003* Diffuse cortical atrophy Mean bifrontal ratio (range)P= 0.345 Mean Sylvian fissure ratio (range) P=0.602 Multivariate analysis of prediction of delayed haematoma evacuation. Maximal thickness P=0.527 OR 2.5 (0.5-41.1) Volume haematoma P=0.01 OR= 1.1 (1.02 -1.17) Midline shift P=0.01 OR=1.43 (1.09-1.89) Cerebral contusion P=0.92 OR 0.85 (0.18-3.97) SAH P=0.43 OR 0.53 (0.11-2.56)	Only patients with subdural- have been shown to high risk in other studies. The neurosurgical rate for these injuries appears v. high ?length of follow up. These patients have been discharged and then undergone reimaging as outpatients. Doesn't preclude early discharge of some of these patients but they will need to be followed up.
Overton et al 2014 USA Can trauma surgeons manage mild traumatic brain injuries? Journal: American Journal of Surgery	Level 1 Trauma centre 2006-2012 Inclusion criteria: • Intra-cranial bleed less than 1 cm • to hospital • GCS13-15 on arrival to ED Excluded: • Multiple injuries on CT • Transferred to other care facility • Left against advice Doesn't state only adults but results presented only for adults.	Retrospective Cohort Study **Aim** Reports initial experience with the management of MTBI by trauma surgeons alone. Hypothesize that patients with MTBI managed by trauma surgeons will be the same as outcomes for patients managed by neurosurgeons.	Outcome measured GOS score at discharge 1= death 2=severe disability 3=mod disability 4= full recovery **Method** Mulitvariate regression analysis to assess whether admission under trauma surgeons affected likelihood of GOS >3 (good recovery)	trauma versus neurosurgical management age, sex, race/ethnicity, injury severity, insurance status GCS	171 patients 8 deaths 4 severe disability 24 moderate disability Neurosurgeons managed 120 Trauma surgeon 51 Multivariate regression analysis to predict GOS >3 (full recovery) Admission Trauma surgeon P=0.3OR 1.74(0.61–4.92) Age P<0.001 OR0.94 (0.91–0.96) ISS P<0.001 OR0.87 (0.81–0.94) GCS P=0.005 OR13.96(2.23–87.3) Other factors in model but no results reported: sex, ethnicity, ISS, insurance status Mean/median GCS=14.7 Mean/median age= 49	**Study Recruitment: Mod risk** Retrospective case note review- depends on information being recorded correctly. Only patients with bleed less than 1cm **Attrition: Mod risk** Not clear when outcomes measured- if at discharge low risk **Prognostic factor measurement: Low risk** Doesn't explain how CT reports interpreted and how 1cm cut off decided. **Outcome measures: mod risk** States GOS- but not when or who determined score ?self reported **Confounding Factors: Mod risk** None obvious **Statistical techniques: Mow risk** States backward step binary logistic regression analysis performed to assess trauma surgeon versus neurosurgical admissions-

						controlled for age, sex, race, ISS, insurance status and GCS motor scores- presents the analysis for only some of these. **Overall** Limited by inclusion criteria of less than 1cm and even though no difference in outcomes with who patients were admitted under, potentially the patient groups received different care.
Schwed et al 2016 California USA	UCLA California Level 1 trauma centre 2012-2015 Inclusion criteria: • Patients identified on trauma registry and case note review • Initial GCS13-15 • Intra-cranial bleed any variety identified by CT imaging Excluded: • Transfers • Not admitted to ICU • Required emergent neurosurgery • Patients less than 18 • In police custody • Pregnant	Retrospective cohort study **Aim** Identify admission variables associated with favourable outcomes with mTBI and intra-cranial haemorrhage **Method** Univariate and multi-variate regression analysis prediction of "favourable outcome composite measure"	**Favorable outcome-** composite outcome of following: Alive at discharge ICU admission for less than 24 hours No in hospital complications Did not require neurosurgery Failed to achieve this if required ventilation or ionotropic support at any point.	Vital signs AIS ISS CT findings-Marshall and Rotterdam scores	380 TBI patients in study period 19 missing records 201 remaining cohort met inclusion/exclusion criteria 4/201 deaths (2 attributable to bleed progression) 129/201 GCS15 6/201 neurosurgical outcomes 21% (42) in hospital complication 78/201=met conditions favourable outcome 0/1 EDH favourable outcome 1/4 ICH favourable outcome 18/36 SDH favourable outcome 30/57 SAH favourable outcomes 22/83 mixed lesions favourable outcome 123/201=unfavourable outcome Univariate comparison between patients with favourable and unfavourable outcomes: Age P=0.01 ISS P=0.001 Head AIS P=0.026 Time to first head CT (hours) non-significant ED systolic blood pressure P= 0.01 ED heart rate P=0.48 Marshall score P=0.11 GCS at time of admission ICU P <0.0001 GCS 15 at admission P=0.0001 Type of hemorrhage Epidural P=0.42 IVH P=0.55	**Study Recruitment: Mod risk** Only admitted to ICU- higher risk group than total population. **Attrition: Low Risk** Only inpatient measures **Prognostic factor measurement: Mod risk** Does not assess pupillary response or anticoagulation/antiplatelets **Outcome measures: Mod risk** Only inpatient related outcome measures. **Confounding Factors: Mod risk** Cohort includes patients with multiple injuries- 2 deaths appear due to factors unrelated to head injury **Statistical techniques: Mod Risk** Selective reporting of significant results. Does present statistical comparison between the groups with favourable and unfavourable outcomes

					SDH P=0.1 SAH P=0.02 Combination P=0.002 All factors statistically significant in univariate analysis were assessed in multivariate analysis Multivariate model predicting favourable outcome: including ED BP, Marshall score, Isolated SAH, Head AIS, ISS<25, GCS15 at ICU admission and age<55 GCS 15 at ICU admission OR 5.5 95% CI (1.6-18.8) P=0.006 Isolated SAH 5.1 95% C.I. (1.5-17.6) P=0.01 Age<55 OR 3.5 95% C.I. (1.1-11.2) P=0.03 Mean/median age= 60	
Thorson et al 2012 Miami USA	Miami Level 1 trauma centre 1996-2010 Inclusion criteria: • Initial GCS13-15 • Present on trauma registry • Head abbreviated AIS 1 or greater • No other injuries (AIS=0 other body regions) • Repeat CT head scan if intracranial injury detected. (4-6 hours after initial CT). Note neurosurgeons decided	Retrospective cohort study **Aim** To test whether routine CT imaging in mTBI with detected intra-cranial injuries provides useful information in the absence of neurological deterioration **Methods** Step wise multi-variate regression for factors P<0.2 associated with progression on CT and craniotomy	Progression of initial lesion or new lesion identified. Neurosurgical intervention. Death.	CT findings-including type of injury, presence of oedema, mass effect or herniation. Age Sex ISS GCS Abnormal neurological examination-change in GCS greater than 1, GCS less than 13,Neurological deficit, or significant symptoms including headache, lethargy, visual disturbance.	1510 patients with GCS13-15 and head injury 537/1510 +ve initial CT scans 62 proceeded immediately to surgery and 115 no repeat CT in 24 hours- (mostly as the neurosurgeon deemed injury insignificant). 360/537 had repeat CT imaging. 11% of repeat CT scans-recalled (i.e.no actual injury) 108/360- progression on CT imaging Mean/median GCS=14.5 Mean/median age= 47 Percent anticoagulated=3 Age No change 46 SD 20 Progression 50 D 23 P=0.13 Sex No Change Male 178 Progression 79 P0.11 Intubated No Change 22 Progression 17 P=0.05 ISS No change 12 SD 5 Progression 15 SD 6 P<0.01 GCS 15 arrival No Change 158 Progression 37 GCS 14 No Change 65 Progression 43 GCS 13 No Change 31 Progression 28 Anticoagulant Use No Change 17 progression 11 0.29 Aspirin No Change 7 Progression 3 Plavix No Change 1 Progression 2 Coumadin No change 2 Progression 4 LMWH No Change 2 Progression 0 Multiple No Change 5 Progression 2 PT No Change 12.2 Progression 12.6 P= 0.443 PTT No Change 25.2 Progression 24.8 P=0.85	**Study Recruitment: High risk** Neurosurgeon have selected out patients with "trivial" injuries-makes this a higher risk group than population of interest **Attrition: Low Risk** Only inpatient measures **Prognostic factor measurement: Low risk** Loose definition for abnormal neurology **Outcome measures: Mod risk** Only inpatient related outcome measures. **Confounding Factors: Low risk** None obvious **Statistical techniques: Mod Risk** Selective reporting of outcomes in regression model Paper concludes all patients should have a repeat CT as 7/360 patients had neurosurgery based solely on repeat CT head findings.

	whether a lesion was to insignificant to warrant a repeat CT Excluded: • Penetrating trauma • Pregnant • Age<18 • Incarcerated • Transfers				30/360 neurosurgical outcomes Age No Neuro Surg 47 SD 21 Neuro Surg 51 D 23 P=0.97 Sex No Neuro Surg Male 241 Neuro Surg 22 P0.11 ISS No Neuro Surg 13 SD 5 Neuro Surg 17 SD 6 P<0.01 GCS 15 arrival Neuro Surg 180 Neuro Surg 13 GCS 14 No Neuro Surg 100 Neuro Surg 8 GCS 13 No Neuro Surg 50 Neuro Surg 9 Anticoagulant Use No Neuro Surg 22 Neuro Surg 6 0.024 Aspirin No Neuro Surg 9 Neuro Surg n 3 Plavix No Neuro Surg 2 Neuro Surg 2 Coumadin No Neuro Surg 2 Neuro Surg 4 LMWH No Neuro Surg 2 Neuro Surg 0 Multiple No Neuro Surg 4 Neuro Surg 2 PT No Change 12.1 Progression 12.0 P= 0.35 PTT No Change 25 Progression 27.5 P=0.45 7/30 operated patients solely on basis of worse CT (no prior neurological decline) 22/360 deaths Logistic regression analysis: unclear which factors were tested in the model Predictors of worse 2nd CT AU ROC curve 0.703 GCS=13 OR4 95% CI 2.02-7.93 P<0.001 GCS=14 OR 3.11 95% CI 1.77-5.48 P<0.001 ISS OR 1.07 95% CI 1.02-1.11 P<0.001 Mass effect OR 2.02 2.02-3.78 P<0.001 Predictors of craniotomy: AUC ROC 0.849 Initial mass effect OR 5.24 95%C.I. (1.96-14.1) P=0.001 New/worse EDH 2nd CT OR 23.3 3.67-148.3 P=0.001 New/worse mass effect 2nd CT 5.73 95% 1.64-20) New/worse herniation 32.1 95% C.I. 7.83-131.6 P=0.001	Possibly include but is a higher risk population given selection out of patients with "non-significant" findings. Note also 11% of 360 repeat CTs recalled-i.e. initial finding not present (4/6 hours after injury).
Quigley et al 2012 Pennsylvania USA	Pennsylvania Level 1 trauma centre 2004-2011 All patients admitted ICU for at least overnight observation	Retrospective Cohort Study **Aim** To assess if traumatic subarachnoid haemorrhage more benign form of mTBI	Discharge home Clinical deterioration CT progression Neurosurgery	Demographics Mechanism of injury Number and results of follow up CT Length of hospital and ICU admission ISS CTs re-reviewed by study radiologist	547 patients identified as subarachnoid 478/547 isolated subarachnoid 470/478 repeat CT imaging 15/470 worse CT (1 is new stroke) 342/478 discharged home 51/478 discharged rehab or nursing home 4/478 self discharge 4/479 long term care facility	**Study Recruitment: Low risk** Identified from prospective trauma registry- dependent on how accurate this is **Attrition: Mod Risk** Not clear whether and when all patients followed up but presents outcomes from outpatient clinic

	Inclusion criteria: • Present on trauma registry • Initial GCS13-15 • Isolated subarachnoid haemorrhage • Does not state adult only but mean age 65.7	Multivariable analysis computed with step-down logistic regression- discharge home primary outcome			1/479 other facility 1/479 to hospice 6 week follow up 1/478 bilsteral subdural- drained States surgical intervention 0.2% Step down Multivariate regression with outcome discharge home Age P<0.0001 Admission GCS P=0.0018 ISS P=0.0088 Not progression of bleed on CT	**Prognostic factor measurement: Low risk** Ct scans reviewed **Outcome measures: Mod risk** Not clear if uniform outpatient followup **Confounding Factors: High risk** Clearly an old patient population- discharge to rehab/nursing home like related comorbidities or other injuries **Statistical techniques: High Risk** Selective reporting of outcomes in regression model No confidence intervals or odds ratios. No explanation of high the model was derived **General comments:** Discharge outcomes contradict low level of intervention. Unable to pool risk factors as are. Can pool to confirm Subarachnoids are low risk.
Velmahos et al 2006 Massachusetts USA	Massachusetts Level 1 trauma centre 2003-2004 All patients with intra-cranial injuries identified reviewed by a neurosurgeon and repeat CT scheduled within 24 hours. Inclusion criteria: • Present on trauma registry	Retrospective cohort study Comparison univariate characteristic patients with worse CT scans compared with the same or improved. Where P value 0.2 or less included in stepwise logistic regression model	Surgical or medical intervention following repeat CT (caniotomy, ICP monitoring, intubation or mannitol, increased ventilation, CSF drain, sedation, transfer to ICU) Worse repeat CT	Demographics ISS Admission observations Time interval between admission and 1st CT and subsequent CT scans	692 patients had CT for head injury 179/692- for scheduled repeat CT 154/692 repeat CT due to intracranial injury 25 no lesion- repeat CT due to anti-coagulation 37/154 worse CT 7/154- medical or surgical intervention due to deterioration 4/154 neursourgical 8/179 deaths 1/44 subdurals neurosurg 0/33 SAH neurosurg 1/13 intra-parenchymal neurosurg 0/7 extra-durals 2/57 multiple neurosurgical Male P=0.44	**Study Recruitment: Low risk** Identified from trauma registry- dependent on how accurate this is Standard model of care for all patients **Attrition: Low Risk** Appears only inpatient outcomes **Prognostic factor measurement: Mod risk** Assessment of time to CT- not clear biological mechanism how this affects outcome or how measured **Outcome measures: Mod risk**

	• Initial GCS13-15 • Blunt head injury • Repeat CT for intra-cranial injury • Presumably adults age presented as mean 48 and SD 25				Age (years) P0.01 ≤65 P<0.01 Mechanism of blunt trauma P= 0.31 Fall Road traffic accident Other 0.31 Injury Severity Score P=0.01 ISS>16 0.09 Glasgow Coma Scale score on arrival P=0.02 Systolic Blood Pressure on arrival (mm Hg) P= 0.63 Anticoagulation therapy P=0.25 Time from arrival to CT P<0.01 First head CT findings solitary or multiple findings P<0.01 Time between first and second CT P=0.10 Stepwise logistic regression model to predict worse CT Time from injury to CT <90 mins OR6.37 95% CI 2.29-17.76 P<0.1 Age>65 OR3.33 95% CI 1.29-8.60 P=0.01 GCS<15 OR 3.13 95% 1.23-8.01 P=0.02 Multiple lesions OR 11.03 95% CI 1.32-92.06 P=0.03 AUC ROC curve 0.83 If all 4 factors present 83% chance worse CT If none present 2% chance worse CT Mean/median GCS=14.7 Mean/median age= 51 Percent anticoagulated=10	Takes reports from attending at face value. Does not report deaths as a primary outcome but included in table- not clear what the cause of deaths is. **Confounding Factors: High risk** Not isolated head trauma and no selection out of comorbid patients- does not appear deaths related to head injury but clear **Statistical techniques: Mod Risk** Selective reporting of outcomes in regression model **General comments:** Time to initial CT highly significant- slightly odd for this study population- not examined any other study. No explanation for deaths given in paper.
Fabbri et al 2013 Italy- multicenter	Multi-centre 32 Italian hospital- both specialist and general 2009 Inclusion criteria: • Any GCS • 18+ • Head abbreviated AIS 1 or greater • No indication for	Retrospective multicentre cohort study **Aim** To assess whether pre-injury antiplatelet use lead to worse outcome in patients with intra-cranial injuries detected by CT imaging	Worse repeat CT defined as increase point on Marshal criteria within 24 hours Neurosurgery within 7 days GOS at 6 months	Age Sex Mechanism Coagulation GCS Anti-platelet medications Type of injury on CT Marshal Classification	Study of all GCS patients but present data for GCS14-15: 1123/1558 patients GCS14-15 Antiplatlet therapy increased the risk of a worse CT: When 2 or less lesions RR 1.86 95% CI 1.06-3.30 P=0.032 When 3+lesions RR 3.34 95% CI 1.74-6.40 P=0.003 87/1123 Worse Characteristic on CT Mean/median age= 65	**Study Recruitment: Mod risk** The paper is not clear about how patients were identified and data extracted Also patients requiring emergency surgery within 7 days based on initial CT excluded- may select out higher risk groups- in practice excluded Marshall 5/6 patients which is reasonable **Attrition: Low Risk** No loss to follow up and standard care for all patients to be reviewed at 6 months

	neurosurgery within 7 days • Marshal category 2-4 • Within 24 hours of injury Excluded: • Need immediate neurosurgery • GCS 3 fixed dilated pupils • Unclear history of mechanism • Hypotension< 90 systolic • Penetrating Injuries • Discharge against medical advice					**Prognostic factor measurement: Low risk** Scans all re-reported **Outcome measures: Low risk** Good outcome end points **Confounding Factors: Mod risk** Not isolated head trauma and state no need to control for comorbidities as shown not to affect head injury outcome **Statistical techniques: Low Risk** Appropriate and well presented **General comments:** Good study Fabbri previously shared data- ?request GCS13-15 subset
Shih et al Taiwan 2016	Tertiary referral Teaching hospital Taiwan No time frame given Inclusion criteria: • Acute TBI and intracranial haemorrhage (epidural, subdural, intra-cerebral or SAH) • Adult- age range 15-75 in study Excluded: • Penetrating injury • GCS<13 • Immediate neurosurgery • Chronic bleed	Retrospective cohort study **Aim** Determine the potential risk factors of delayed neurosurgical intervention in mTBI with intra-cranial haemorrhage Stepwise logistic regression to identify variables that predicted failure of conservative treatment	Neurologic deterioration-GCS drop 2+ points, seizures, signs raised ICP Repeat CT if deterioration- whether worse Neurosurgical intervention- including craniotomy, craniectomy	Sex Age Mechanism of injury GCS ISS Laboratory results including clotting CT results as reviewed by investigator	340 patients met inclusion criteria 13/340 neurosurgical outcomes 25/340 neurological decline 7/118 mixed lesions neurosurgery 34/340 worse CT 3/340 died Univariate analysis: delayed neurosurgery versus non-neurosurgery Median age P=0.082 Male/female P=0.573 OR 0.648 95% CI 0.196–2.149 GCS P= 0.189 Anti-platelet and/or warfarin therapy P=0.403 OR 2.188 95% CI 0.263–18.222 Statin therapy P= 1.000 Hypotension 0 4 P= 1.000 WBC count (1000/mL)P= 0.023 RBC count (1000/mL) p=0.401 Hemoglobin, P=0.606 Coagulopathy P=1.000 Hypertension P=0.526 OR 0.484 95% CI 0.105–2.228 Diabetes mellitus P=1.000 OR 1.028 95% CI 0.221–4.780 (!?)0 Old cerebral vascular accident=1.000 Coronary artery diseases P=1.000 Arrhythmia P=1.000	**Study Recruitment: Lod risk** No uniform criteria for which patients undergo immediate neurosurgery- just selected by neurosurgeon **Attrition: Low Risk** Only inpatient measure **Prognostic factor measurement: Low risk** Scans all re-reported **Outcome measures: Mod risk** Only inpatient measures- potential for discharge and deterioration **Confounding Factors: Mod risk** Not isolated head trauma **Statistical techniques: Mod Risk**

	All patients reviewed by neurosurgeon who determined whether for immediate neurosurgery or conservative management				Liver cirrhosis P=1.000 Chronic renal disease P=1.000 Renal failure P=1.000 ISS score, Median P=0.005 Single intracranial heamorrhageP=0.149 Multiple intracranial heamorrhage P=0.149 EDH P ≤0.001 OR 9.923 95% CI 3.105–31.708 SDH P=1.000 OR 0.906 95% 0.298–2.753 IPH P=0.366 OR1.812 95% CI 0.594–5.526 SAH P=0.044 OR0.251 95% CI 0.068–929 IVH P= 0.111 OR13.542 95% CI 1.147–159.876 Midline shift P≤0.001 OR19.813 95% CI5.495–71.435 Skull fracture P≤0.001 OR21.750 95% CI4.707–100.510 Pneumocranium P=0.621 Volume of EDH P≤0.001 Volume of SDH P=0.092 Volume of IPH P=0.657 Stepwise logistic regression: model included WBC count, midline shift, skull fracture large volume EDH and higher ISS- significant predictors of delayed neurosurgery. Volume of extra-dural haemorrhage associated with delayed neurosurgery Increase volume EDH 1 cubic cm increase risk of neurosurgery by 16% (p=0.022 OR 1.190 95% CI 1.041-1.362) AUC volume EDH=0.917 (95% CI 0.797-1.00) Mean/median GCS=14.7 Mean/median age= 50	Mod risk selective reporting of significant prognostic factors. Does not report whole model. Also some apparent mistakes in univariate analysis **General comments:** Does not report outcomes by single lesion type
Bardes et al 2016 USA	Level 1 trauma centre West Virginia 2009-2011 All mTBI patients with bleeds admitted to general surgical ICU with a neurosurgical consultation Inclusion criteria: • Blunt TBI • Age>18	Retrospective Cohort study **Aim:** Identify low risk mTBI patients with intra-cranial bleeds that do not require admission to ICU	Documented neurological decline Medical intervention Neurosurgical intervention	Admissions GCS GCS 6, 12, and 24 hours Type of bleed Bleed progression on CT Aspirin Clopidogrel Warfarin Admission Coag ISS	389 patients met inclusion criteria 5.1% (20) in hospital mortality 53/389 patients neurological decline 376/389 scheduled repeat CT 69/376 worse CT 35/389 craniotomy 46/389 patients required medical or neurosurgical intervention Univariate comparison patients with decline versus no neurological decline GCS<15 P=0.002 SDH P=0.0025 Age≥55 P=0.001 Use Warfarin P=0.039 ISS P=0.22 AIS=P=0.12 SAH P=0.15	**Study Recruitment: Lod risk** Representative sample of population of interest. Limitations of retrospective data collection **Attrition: Low Risk** Only inpatient measure **Prognostic factor measurement: Low risk** Scans not re-reported **Outcome measures: Mod risk** Only inpatient measures- potential for discharge and deterioration

	• GCS13-15 • ISS<25 Excluded: • Penetrating injury • GCS<13 States in results all patients had evidence of intra-cranial haemorrhage on bleed- doesn't define what this includes				EDH P=0.18 ICB P=0.051 Aspirin P=0.54 Clopidogrel P=0.17 PT P=0.042 aPPT P=0.0028 Admision INR P=0.42 Decision tree subgroup analysis: No GCS15 patient ≤ 55 underwent neurological decline= low risk group Mean/median GCS=14.8 Mean/median age= 63 Percent anticoagulated=12	**Confounding Factors: Mod risk** Not isolated head trauma or control for comorbidities Does use ISS to exclude severe polytrauma **Statistical techniques: Mod Risk** Mod risk selective reporting of significant prognostic factors. Does not present decision tree analysis transparently
Sharifuddin et al 2012 Malaysia	Patients admitted under neurosurgeons 2008-2009 specialist centre Inclusion criteria: • GCS 13-15 • 12 years and older • positive initial head CT • isolated blunt head injury • presented within 24 hour of initial injury Excluded: • previous history of head injury • on anticoagulation therapy (aspirin, heparin or warfarin) • polytrauma	Prospective observational study Aim To evaluate whether the repeat head CT were useful in providing information that leads to any neurosurgical intervention	Repeat CT at 24-48 hours as categorized: Unchanged (no change could be assessed based on the size of the injury), Improving (resolution or improvement based on the size of the injury) Worsened (increase in size or evidence of new intracranial lesion). Surgical interventions: craniotomy, intracranial pressure monitor placement or intubation.	Sex Age (years) ≥ 65 years Ethnic groups Mechanism of injury: MVA/Fall/Other Admission GCS Associated symptoms Post-traumatic amnesia Headache Vomiting Dizziness Type of injury identified	279 patients met the inclusion criteria Neurological decline 66 patients (23.7%) Worse CT in 58 patients (20.8%). 31 (11.1%) patients neurosurgical outcome. 3 deaths. Univariate comparison patients with progression on CT and without: Male P=0.189 Age ≥ 65 P < 0.001 Ethnic groups P=0.624 Mechanism of injury MVA versus others P=0.333 GCS<15 P=0.003 Post-traumatic amnesia P=0.069 Headache P=0.019 Vomiting P=0.441 Dizziness P=0.262 Multiple lesion P=0.001 Base of skull fracture P=0.865 Convexity fracture P=0.842 Hb (g/litre) on admissionP0.009 INR on admission P=3 0.388	**Study Recruitment: Low risk** Retrospective case note review- depends on accuracy of notes. Not clear if all patients with ICH admitted under neurosurgeon- potential for selection of high risk population. Note age 12+ does not strict meet inclusion criteria. **Attrition: Low RIsk** Outcomes only during hospital admission- no loss to F/U **Prognostic factor measurement: Mod risk** The mechanism of injury- doesn't discriminate between high and low risk mechanisms. CT interpreted once by attending radiologist or neurosurgeon. No quality control. **Outcome measures: low risk** As reported outcomes of worse CT, neurosurgery or death as an inpatient low risk for bias. However, no follow up outcome measures for delayed deterioration. **Confounding Factors: Mod risk**

	• Major comorbidity • suspected drug or alcohol intoxication, • Neurological impairment trauma • Immediate neurosurgery • Admitted ICU for close observation				Stepwise multiple logistic regression model Risk factors for progression on CT: Age ≥ 65 P<0.001 95%C.I. (0.098- 0.364) Multiple lesions on initial CT P=0.018 95% C.I.(0.239- 0.877) GCS score < 15 P= 0.016 95% C.I. (1.164 - 4.333) 44/144 multiple lesion worse CT Mean/median GCS=14.6 Mean/median age= 39 Percent anticoagulated=0	Possibility of anti-coagulants. Not recorded. **Statistical techniques: Mow risk** Stats do not present what the risk measure is- presumably an OR. Also selective reporting of significant results. Only for progression on CT- dubious value
Sumritpradit et al 2016 Bangkok Thailand	Patients admitted to an Acute Care Unit surgery 2009-2013 Inclusion criteria: • Admission<72 hours • 16 years and older • positive initial head CT • Non-surgical initial management • Includes all GCS score but presents data for GCS13-15 patients • Patients under went repeat CT imaging-determined after neurosurgical review	Retrospective cohort study Aim: To determine the value of repeat CT imaging in TBI for risk stratification of patients	Neurologic deterioration: reduced consciousness, limb weakness, lateralizing signs, severe headache, vomiting, and dizziness. Neurosurgery	Age Sex Co-morbidities Medications Initial GCS AIS Medications CT findings	145 patients matched inclusion criteria 98/145 GCS13-15 74/98 routine repeated CT scans (36/98 worse) (1/74 neurosurgical) 24/98 clinically deteriorated and underwent CT imaging (7/28 neurosurgery) Overall 8/98 GCS13-15 patients neurosurgery 24/98 some clinical deterioration-prompting repeat CT GCS13-15 Univariate comparison patients underwent neurosurgery and did not. Age>50 P=0.478 Mean age P=0.295 Male P=0.706 Traffic injury=0.256 Diabetes mellitus P=0.354 Hypertension P=0.135 Ischemic heart disease P=0.070 Cerebrovascular disease P=0.592 Aspirin =1.000 Warfarin P=1.000 Clopidogrel P=0.017 ISS, mean p= 0.405 ISS > 19 P= 0.282 Brain AIS, mean P=0.080	**Study Recruitment: High risk** Only recruited patients that neurosurgeons had planned a repeat CT scan (293/442 patients with injuries no repeat CT versus 149/442 for repeat CT) Selection bias of higher risk group then all GCS13-15 patients with CT detected injuries **Attrition: Low Risk** Outcomes only during hospital admission- no loss to F/U **Prognostic factor measurement: Mod risk** No outline of how CT scans reported and risk stratified b **Outcome measures: low risk** As reported outcomes of worse CT, neurosurgery or death as an inpatient low risk for bias. However, no follow up outcome measures for delayed deterioration. **Confounding Factors: Mod risk** Does not state how patient with other injuries delt with

					AIS > 4 P=0.073 SBP P=0.240 Heart rate on admission, mean p= 0.095 Epidural hematoma P= 1.000 Subdural hematoma P=0.136 Subarachnoid haemorrhage P=0.464 Hemorrhagic contusion P=0.715 Intraventricular hemorrhage P=1.000 Diffuse axonal injury P=) 1.000 Skull fracture P=1.000 Base of skull fracture=0.409 Midline shift > 2 mm P=0.003 Duration from injury to 1st CT P=0.603 Odds ratios associated with these factors reported separately: Subdural hematoma OR 5.3 95%CI (0.63–45.33) P=0.136 Hypertension OR 4.1 95% CI (0.78–21.46) P=0.135 AIS > 4 OR 4.0 95%CI (0.91–17.55) P=0.073 Ischemic heart disease OR 4.8 95% C.I. (0.99–23.19) P=0.070 Clopidogrel OR 10.2 95C.I. (1.87–55.38 P=0.017 Midline shift > 2 mm OR11.9 95% C.I. (2.50–57.20) P=0.003 Neurological deterioration resulting in CT OR 30.0 95% C.I. (3.46–280.83) P<0.001 Mean/median age= 57 Percent anticoagulated=4	**Statistical techniques: Low risk** Presents simple univariate analysis between neurosurgical and non-neurosurgical patients Is a higher risk population due to selection for repeat CT imaging- possibly unable to include in any meta-analysis.
Sifri et al 2006 New Jersey USA	New Jersey Level 1 trauma centre 2002-2003 12 months Inclusion criteria: • Initial GCS13-15 • Intra-cranial bleed- intra-cerebral, extra-dural, subdural subarachnoid or contusion Excluded: • Previous brain surgery or	Prospective Cohort Study **Aim** Prospectively assess the value of a repeat CT in patients with mTBI and intra-cranial haemorrhage and normal neurological examination Repeat CT within 24 hours	Neurosurgery following second scan Admission to ICU or administration of mannitol following second scan In hospital mortality. GOS at discharge. Discharge destination	Abnormal neurological examination prior to repeat CT (GCS<15 or severe headache/vomiting/ gross motor or sensory deficits) Sex Age GCS Mechanism Type of injury identified by CT	161 patients GCS13-15 with intra-cranial bleed 10 excluded due to co-morbidities. 5 required immediate neurosurgery 16 did not undergo repeat imaging 130 in study population 99 normal neurology at time of repeat CT; 31 abnormal neurology at time of repeat CT. 0/99 neurosurgery 1/99 death (unrelated to intra-cranial injury) 13% 99 CT scans worse 2/31 neurosurgery 5/31 deaths 14/31 repeat CTs worse Abnormal neurological exam predicts changes repeat CT OR 5.28 CI2.08-13.4 P=0.002	**Study Recruitment: Mod risk** Only patients with repeat CT- likely to be a higher risk group **Attrition: Low Risk** Only inpatient measures **Prognostic factor measurement: Mod risk** Does not try and grade severity of CT findings as predictor. Loose definition for abnormal neurology- sometimes prompted repeat CT and no uniformed time when all CT scans performed. **Outcome measures: Mod risk**

	cerebral pathology or chronic neurological condition like dementia • Concurrent spinal injury • Anti-coagulated or existing clotting disorder • Patients that underwent immediate or planned neurosurgery due to first CT Patients that only underwent 1 CT				Mean/median GCS=14.6 Mean/median age= 45 Percent anticoagulated=0	Only inpatient related outcome measures. **Confounding Factors: Mod risk** Cohort includes patients with multiple injuries and abnormal observations **Statistical techniques: Low Risk** Minimal statistical analysis
Bee et al 2009 Tennessee USA	Level 1 trauma centre 2005-2007 Identified from trauma registry All patients admitted to ICU under neurosurgeon and received a repeat CT scan Inclusion criteria: • mTBI • Blunt trauma to head • GCS 14-15 • Intra-cranial injury CT head Excluded: • Facial or skull fractures • Immediate neurosurgery	Retrospective cohort study **Aim** Assess whether repeat CT imaging and ICU admission necessary in mTBI with intra-cranial injury	Worse CT Clinical examination change Neurosurgical intervention	Age Sex Admission observations AIS ISS Admission GCS	207 patients met inclusion criteria 58/207 worse CT or neurology requiring intervention (4 neurology only) 31/77 patients multiple/mixed lesions worse CT 18/207 neurosurgery 2 deaths (1 due to stoke other following craniotomy) 5/18 neurosurgical= subdurals with no clinical change but worse CT Univariate Comparison Worsening CT or worsening neurology requiring an intervention versus no deterioration (58 versus 149) Average age worse 47 (47.2 +/-19.8) No worse 45 (45.5+/- 18.7) P=0.56 Average admission SBP worse 152 (152.3 +/-28.3) No worse 143 (143.1+/- 25.9) P=0.03 Average admission pulse worse 87 (86.9 +/-15.3) No worse 88 (88.5+/- 16.1) P=0.556 Average HAIS worse 4.2 (4.21 +/-0.55) No worse 3.8 (3.84+/- 0.54) P<0.0001 Average ISS worse 22.3 (22.3 +/-6.25) No worse 19.6 (19.6+/- 6.9) P=0.018 Mean/median age= 46	**Study Recruitment: low risk** Dependent on accuracy of trauma registry **Attrition: Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium** risk No re-reporting of CTS **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for comorbidities **Statistical techniques: Low Risk** Higher rates of adverse outcome than other studies

	• Other injuries requiring ICU admission Data only presented for adults (15-94)					
Darby MSc Thesis 2015 USA	Level 1 trauma centre California 2007-2011 Patients identified on a hospital trauma registry Inclusion criteria: • Initial GCS13-15 • Blunt head trauma • Positive CT scan. • 2 or more CT scans • 18+ Excluded: • Pregnant • Age<18 • Penetrating injury	Retrospective Cohort Study: To assess whether GCS 15 patients with intra-cranial haemorrhage that maintain a GCS of 15 benefit from routine CT imaging	Worse repeat CT imaging Neurosurgical outcomes	Age/ Age 65 + Anti-coagulant Medication ISS LOC Skull fracture displaced/undisplaced Neurological symptoms Time interval between scans GCS/deterioration in GCS	658 patients GCS13-15 with positive CT scans 88 incomplete notes 201 only 1 CT scan Study population 369 patients with at least 2 CT scans. 111/369 GCS 15 at presentation and throughout. 0/111 neurosurgery 20.7% of 111 worse CT 0.9% mortality 258 GCS<15 at some point during hospital admission 37.6% 258 worse CT 11/258 neurosurgery 2.7% 258 deaths Overall 11/369 neurosurgical interventions Mean/median age= 53 Progression of Injury: Unstable GCS < 15 Unadjusted OR 2.21 (95% C.I. 1.33-3.68) adjusted 1.71 (95 % C.I.1.00-2.91) P=0.05 ISS Unadjusted 1.04 (95% C.I. 1.01-1.07) Adjustede 1.1 (0.99-1.05) P=0.27 Age Unadjusted1.01 (95% C.I. 1-10.2) Adjustede 1.01 (0.99-1.02) P=0.08 Anti-coagulation Unadjusted 1.02 (95% CI 0.59-1.77) Adjusted 0.76 (0.40-1.47) P0.42 Risk of Neurosurgery Unstable GCS unadjusted 4.16 (0.51-33.63) adjusted 2.98 (0.35-25.18) P=0.32 ISS Unadjusted 1.04 (1.01-1.07) adjusted 1.05 (0.99-1.12) P=0.10 Age Unadjusted 1.01 (1.00-1.02) ajusted 1.11 (0.96-1.28)	**Study Recruitment: High risk** Approximately 1/3 of patients with injuries detected by CT imaging not included either because incomplete or only 1 CT scan. Patients on which multiple scan conducted likely to be higher risk. **Attrition:Low Risk** Low risk- inpatient outcomes **Prognostic factor measurement: Medium risk** No re-reporting of CTS Does not include CT findings as a prognostic factor. **Outcome measures: Medium risk** No outcome measures after discharge **Confounding Factors: Medium risk** No control for comorbidities **Statistical techniques: Mod Risk** Performs different analysis for neurosurgical outcomes compared to worsening CT scans.

Fabbri et al 2008 Italian	District general hospital rural Italy Prospective recruitment from 1999-2006 Inclusion criteria: • Admission GCS score ≥ 9 • Age over 10 • Initial head CT scan positive for any type of trauma • Initial non-operative management. Excluded: • Persistent hypotension caused by additional injuries • Patients requiring immediate surgery • Penetrating injuries • Patients that have been intubated	Prospective cohort study Aim: Evaluate the effects on outcome of a model based on observation in a neurosurgical unit versus observation in a peripheral hospital with neurosurgical expertise via a teleradiology system and a NSU transfer time of 30–60 min	Follow up GOS at 6 months (includes mortality). Neurosurgical intervention within 7 days.	Age, Coagulation status, Charlson Co-morbidity Index, Injury Severity Score GCS CT scan results-Marshall category Type of Injury	N=718 GCS13-15 patients age>12 Anonymised individual patient made available by authors and used for analysis.	

Appendix 23: Data Extracted from Included Studies

Papers deriving and validating the BIG criteria N=3 (not included in meta-analysis)

Reference	Population	Study Design	Outcome Measures	Prognostic factors assessed	Results	Quality Appraisal
Joseph et al 2014 USA Study 1: defining the BIG criteria	Level 1 Trauma centre 2009-2011 Inclusion criteria: • All TBI patients with CT findings = skull fracture/ ICH Exclusion Criteria: • Transfer or patients requiring emergent surgical intervention Categorisation of these patients into 3 criteria-derived through local consensus BIG 1 (discharge after 6 hours obs from ED): • GCS 13-15, normal pupils and no focal neurological deficit • Not intoxicated • not anti-coagulated or anti-platelets • single ICH <5mm and no skull fracture single IPH BIG 2 (admit to hosp. not neurosurgeon) • GCS 13-15, normal pupils and no focal neurological deficit • Can be intoxicated • Non-displaced Skull fracture	Retrospective Cohort Study- Aim: Define guidelines for based patients' history, examination and initial CT head findings regarding which patients require observation in ED, RHCT or neurosurgical consultation. Local consensus for categories	Neurosurgical intervention Progression of CT findings on a repeated scan Neurological deterioration if BIG 1 or 2- GCS<12, abnormal focal neurology or abnormal pupils	Anticoagulation Anti-platelets OBS on admission to ED GCS Intoxication CT head scans all reviewed by a single investigator to give size of bleed and associated findings	1232 patients TBI with positive CT scan 121=BIG 1 313=BIG 2 798=BIG 3 888/1232 underwent repeat CT 13% (159) patients neurosurgical outcome- all in BIG 3 category. No BIG 1 patients had neurological deterioration No Big 1 patient worsening CT 2.6% (9) BIG 2 patients worsening CT 2/313 BIG 2 patients deteriorated neurologically- transferred to neurosurgical care. No BIG2 patient needed neurosurgery BIG3 patients 21.6% worsening CT 3% neurosurgical intervention	**Study Recruitment: Low risk bias** Retrospective cohort review- reliant on accuracy of written notes. Cohort identified by case note review but no details of how this was done- possible selection bias. What constitutes emergent surgical intervention- how many from BIG 1/BIG2 criteria excluded by this. **Attrition: low risk** Inpatient outcomes only **Prognostic factor measurement: Mod risk** Radiology report double checked by one person, only. Definition of neurological deterioration is defined differently as altered mental state and focal deficit and GCS less then 13 in different places. **Outcome measures: Mod risk** No routine follow up of all patients- must re-attend at same hospital to register **Confounding Factors: Low risk** Age affect outcome and size of bleed **Statistical techniques: N/A**

	• Bleed 5-7mm • 2 intra cerebral bleeds 3-7mm • Not anticoagulated or antiplatelets BIG 3 (repeat CT and admit under neurosurgeon HDU) • GCS <13 or abnormal pupils or focal neurological deficit • Taking anti-coagulant or anti-platelets • Multiple types of injury on CT • Bleeds >7mm • Displaced skull fractures • Intubated patients					
Joseph et al 2014 USA Study 2 validating the BIG criteria Identified Search Strategy	March 2012-Dec 2013 Level 1 Trauma centre Inclusion criteria BIG 1 patients: • GCS 13-15, normal pupils and no focal neurological deficit • Not intoxicated • not anti-coagulated or anti-platelets • single ICH <5mm and no skull fracture • single IPH Excluded: • Patients transferred from other hospital • Intubated	Prospective Cohort Study Aim To evaluate the established BIG 1 category for managing patients with traumatic brain injury	Patients remained in ED for observation for 6 hours. If no neurological deterioration- discharged. Repeated neurological assessment every 2 hours- if GCS<13, unequal pupils or focal neurological deficit- neurological deterioration Need for neurosurgical intervention. Need for Repeat CT due to neurological deterioration. Hospital or ICU admission. In-hospital mortality. 30 day readmission	Prospectively recorded: Age Sex Admission observations Neurological assessment of GCS, examination and pupils. Intoxication Anti-platelet or anti-coagulation Intubation LOC Initial CT findings by attending radiologist- confirmed by study radiologist	States 148 patients met criteria prospectively. 127/148 patients included and matched 127 patients with matched characteristics of demographics, medications and CT findings before implementation of BIG criteria. No patients underwent neurosurgery, had neurological deterioration or died, both of the 127 prospectively recruited and those matched retrospectively. Statistically significant reduction in hospital admissions, ICU admissions and repeat CT imaging in prospective cohort post implementation of BIG criteria.	**Study Recruitment: mod risk** States GCS13-15 and range presented as GCS13-15 but also excludes unexaminable patients and patients with altered mental state- appears cohort does not contain all GCS 14 and 13 patients. Not clear about how the cohort was prospectively recruited. **Attrition: mod risk** Disregards 21 of recruited cohort in analysis to match with retrospectively available patients. **Prognostic factor measurement: Mod risk** Reliability of case notes- may be incomplete The definitions of bleed size are subjective. Abnormal focal neurology is subjective and clinician dependent. CT scan re-reviewed by a single researcher- possible bias. **Outcome measures: Mod risk** Measures: no structured follow up of every patient. Patients could have been discharged and died in the community-

	• Patients undergoing emergent neurosurgical intervention • Unexaminable patients				0 30 day readmissions although 5 ED visits	study would have missed this. States over 50% admitted but that all discharged from the ED in the abstract. **Confounding Factors: Mod risk** Age not part of BIG1 but could affect outcome and size of bleed **Statistical techniques: N/A** General Points: Small numbers of patients in this specific setup. Would support small CT findings low risk, but risk stratification very dependent on accuracy and consistency of radiology report.
Joseph et al 2015 USA Study 2:further validation of BIG criteria	Pre BIG TBI March 2011-Feb 2012 Post BIG July 2012-June 2013 Level 1 Trauma centre Inclusion criteria: • All patients with blunt trauma mechanism and ICH/Skull fracture Excluded: • Transfers • Dead on arrival • Needed immediate neurosurgery. Presents subgroup analysis of BIG 1 patients Inclusion criteria BIG 1 patients: • GCS 13-15, normal pupils and no focal neurological deficit • Not intoxicated • not anti-coagulated or anti-platelets	Prospective cohort study Compare outcomes in TBI before and after implementation of BIG criteria	Number of routine repeat CT head scans Neurosurgical consultations Progression of bleed on CT Neurosurgical intervention during hospital admission (craniotomy, craniectomy ICP monitoring) ICU admission 30 day readmission	Prospectively recorded: Age Sex Admission observations Neurological assessment of GCS, examination and pupils. Intoxication Anti-platelet or anti-coagulation Intubation LOC Initial CT findings by attending radiologist-confirmed by study radiologist	Pre BIG 87 BIG 1/415 0 neurosurgery 0 deaths 3 progression on CT 68 (78%)admitted 24 (27.5%) admitted ICU 76 (87.4%) neurosurg consultations 59 (67.8%) repeat CT Post Big 83 BIG 1/381 0 neurosurgery 0 deaths 1 progression on CT 42 admitted (50.6%) 6 ICU admission (7.2%) 7 (8.4%) neurosurg consultation 6 (7.2%) repeat CT Statistically significant (P<0.001 admission hospital, ICU, repeat CT imaging and neurosurgical consultation post introduction of BIG criteria)	**Study Recruitment: Low risk** States all patients with TBI prospectively recorded on data- not cleat how patients identified and recruited. Emergent neurosurgical patients excluded- no definition given **Attrition: low risk** Outcomes only as inpatients or if re-present **Prognostic factor measurement: Mod risk** Ct are reviewed by a member of study group- the cut offs are slightly subjective on CT measurement **Outcome measures: Mod risk** Only measures as inpatient/re-presentation. Potential for discharge and deterioration. **Confounding Factors: low risk** Age **Statistical techniques: Mod risk** Presents data for all patients or BIG 1 patients- not all GCS13-15 patients

	• single ICH <5mm and no skull fracture • single IPH					

Appendix 24: Table of Full Studies Retrieved and Excluded

No.	Study	Reason Excluded
1.	Anonymous et al[103] (Full study revealed duplicate of Corrigendum et al[282])	Unable to differentiate initial GCS13-15 patients
2.	Bajsarowicz et al[106]	Abstract only
3.	Bajsarowicz et al[105]	Unable to differentiate initial GCS13-15 patients
4.	Baldawa et al[107]	Letter about included study
5.	Basahm et al[108]	Unable to differentiate initial GCS13-15 patients
6.	Carlson et al[110]	Included paediatric patients and patients with no injuries identified by CT imaging
7.	Chen et al[111]	Uses lumbar puncture to diagnose brain injury
8.	Choudhry et al[113]	Duplicate study[112]
9.	Flaherty et al[115]	Abstract only
10.	Gore et al[116]	Abstract only
11.	Iaccarino et al[117]	Unable to differentiate initial GCS13-15 patients
12.	Inamasu et al[118]	Unable to differentiate initial GCS13-15 patients
13.	Jacobs et al[119]	Includes patients no injuries on CT imaging
14.	Jiang et al[120]	Included patients of initial GCS<13 Not clear if all GCS13-15 patients have injuries present on CT imaging.
15.	Jiang et al[121]	Included patients of initial GCS<13 Not clear if all GCS13-15 patients have injuries present on CT imaging.
16.	Joseph et al[122]	Unable to differentiate initial GCS13-15 patients
17.	Joseph et al[123]	Unable to differentiate initial GCS13-15 patients
18.	Joseph et al[125]	Unable to differentiate initial GCS13-15 patients
19.	Kim et al[127]	Unable to differentiate initial GCS13-15 patients
20.	Kreitzer et al[129]	Abstract only (full study included[157])
21.	McCutcheon et al[132]	Unable to differentiate initial GCS13-15 patients
22.	Nishijima et al[135]	Abstract only and associated paper included patients of initial GCS<13
23.	Nishijima et al[138]	Unable to differentiate initial GCS13-15 patients
24.	Nishijima et al[139]	Unable to differentiate initial GCS13-15 patients
25.	Penn et al[141]	Abstract only (full study included[109])
26.	Rubino et al[143]	Outpatient Setting
27.	Orringer et al[150]	Unable to differentiate initial GCS13-15 patients
28.	Yuan et al[151]	Unable to differentiate initial GCS13-15 patients
29.	Zare et al[152]	Includes paediatric population
30.	Zhao et al[153]	Not clear about inclusion criteria and definition of non-operative-no response from authors when contacted.
31.	Park et al[154]	Unable to differentiate initial GCS13-15 patients
32.	Schuster et al[155]	Unable to differentiate initial GCS13-15 patients
33.	Smith et al[156]	Unable to differentiate initial GCS13-15 patients
34.	Choudhry et al[159]	Abstract only (full paper included[112])
35.	Tong et al[283]	Unable to differentiate initial GCS13-15 patients
36.	Yadav et al[162]	Unable to differentiate initial GCS13-15 patients and included children

37.	Cohen et al[163]	Includes patients with no injury on initial CT
38.	Stein et al[175]	Theoretical study-no data
39.	Borovich et al[179]	Case reports
40.	Knuckey et al[180]	Pre-1996
41.	Chen et al[181]	Pre-1996
42.	Mertol et al[182]	Case reports pre-1996
43.	Brown et al[184]	Unable to differentiate initial GCS13-15 patients
44.	Fainardi et al[186]	Unable to differentiate initial GCS13-15 patients
45.	Karasu et al[187]	Unable to differentiate initial GCS13-15 patients and includes children
46.	Türedi et al[189]	Includes patients with no injury on initial CT
47.	Connon et al[190]	Unable to differentiate initial GCS13-15 patients
48.	Chang et al[284]	Unable to differentiate initial GCS13-15 patients
49.	Chao et al[192]	Unable to differentiate initial GCS13-15 patients
50.	Sullivan et al[193]	Unable to differentiate initial GCS13-15 patients
51.	Innocenti et al[195]	Includes patients with no injury on initial CT
52.	Muszynski et al[196]	Includes Children
53.	Patel et al[197]	Unable to differentiate initial GCS13-15 patients
54.	Lingsma et al[198]	Includes patients with no injury on initial CT
55.	Wong et al[200]	Case studies and pre-1996
56.	Offner et al[201]	Unable to differentiate initial GCS13-15 patients
57.	Wong et al[202]	Duplicate of 55
58.	Bhau et al[203]	Unable to differentiate initial GCS13-15 patients
59.	Chen et al[111]	Includes Children and patients without CT identified injuries
60.	Gaetani et al[204]	Unable to differentiate initial GCS13-15 patients
61.	Greene et al[205]	Unable to differentiate initial GCS13-15 patients
62.	Son et al[206]	Unable to differentiate initial GCS13-15 patients
63.	Pradeep et al[207]	Unable to differentiate initial GCS13-15 patients
64.	Alahmadi et al[285]	Unable to differentiate initial GCS13-15 patients
65.	Chieregato et al[185]	Includes Children
66.	Kehoe et al[165]	Unable to differentiate initial GCS13-15 patients
67.	Lesko et al[166]	Unable to differentiate initial GCS13-15 patients
68.	Lawrence et al[8]	Includes Children
69.	Roka et al 2008[188]	Includes Children

Appendix 25: Characteristics of included studies

No.	Study	Type	Size	Outcomes	Estimate of Outcome of interest	Univariate of analysis of any Prognostic factor	Multivariable Model of several prognostic factors
1	Sifri et al 2006[146]	Prospective Cohort	130	Death Neurosurgery Progression CT	✓	✓	
2	Brown et al 2007[183]	Prospective Cohort	142	Death Deterioration Neurosurgery Progression CT	✓		
3	Fabbri et al 2008[79]	Prospective Cohort	723	Death Neurosurgery	✓	✓	
4	AbdelFattah et al 2012[100]	Prospective Cohort	145	Death Deterioration Progression CT	✓		
5	Sharifuddin et al 2012[145]	Prospective Cohort	279	Death Deterioration Neurosurgery Progression CT	✓	✓	✓
6	Ding et al 2012[161]	Prospective Trial	32	Neurosurgery Progression CT	✓		
7	Nishijima et al 2014[137]	Prospective Cohort	600	Deterioration Neurosurgery	✓	✓	✓
8	Sifri et al 2004[172]	Retrospective Cohort	202	Death Deterioration Neurosurgery Progression CT	✓		
9	Velmahos et al 2006[148]	Retrospective Cohort	154	Deterioration Neurosurgery Progression CT	✓	✓	✓
10	Huynh et al 2006[167]	Retrospective Cohort	56	Deterioration Neurosurgery Progression CT	✓		
11	Bee et al 2009[169]	Retrospective Cohort	207	Death Neurosurgery	✓	✓	
12	Klein et al 2010[128]	Retrospective Cohort	323	Death Neurosurgery	✓		
13	Schaller et al 2010[30]	Retrospective Cohort	110	Death Deterioration Neurosurgery	✓		

14	Nasir et al 2011[176]	Retrospective Cross sectional	275	Neurosurgery Progression CT	✓		
15	Sifri et al 2011[194]	Retrospective Cohort	107	Deterioration Neurosurgery Progression CT	✓		
16	Levy et al 2011[130]	Retrospective Cohort SAH only	117	Death Neurosurgery Progression CT	✓		
17	Washington et al 2012[149]	Retrospective Cohort	321	Deterioration Neurosurgery Progression CT	✓	✓	✓
18	Homnick et al 2012[174]	Retrospective Cohort	341	Death Deterioration Neurosurgery Progression CT	✓		
19	Nayak et al 2013[133]	Retrospective Cohort	321	Death Neurosurgery Progression CT	✓		
20	Borczuk et al 2013[109]	Retrospective Cohort	404	Deterioration Neurosurgery	✓	✓	✓
21	Almenawer et al 2013[93]	Retrospective Cohort study and meta-analysis	445	Neurosurgery Progression CT	✓		
22	Joseph et al 2013[124]	Retrospective Cohort	270	Death Neurosurgery	✓		
23	Thorston et al 2012[84]	Retrospective Cohort	360	Neurosurgery Progression CT	✓	✓	✓
24	Choudhry et al 2013[113]	Retrospective Cohort	757	Death Deterioration Progression CT	✓	✓	✓
25	Deepika et al 2013[114]	Retrospective Cohort SAH only	34	Unable to extract			
26	Fabbri et al 2013[158]	Retrospective Cohort	1123	Progression CT	✓	✓	
27	Boris et al 2013[177]	Retrospective Cohort	68	Deterioration Neurosurgery Progression CT	✓		
28	Thomas et al 2010[29]	Retrospective Cohort	457	Deterioration Neurosurgery	✓		
29	Nishijima et al 2013[134]	Retrospective Cohort	1412	Deterioration Neurosurgery	✓		
30	Quigley et al 2013[142]	Retrospective Cohort SAH only	478	Neurosurgery Progression CT	✓		✓
31	Levy et al 2014[131]	Retrospective Cohort	76	Deterioration Neurosurgery	✓		

32	Overton et al 2014[140]	Retrospective Cohort	171	Deterioration	✓		✓
33	Phelan et al 2014[173]	Retrospective Cohort SAH only	77	Death Deterioration Neurosurgery Progression CT	✓		
34	Kreitzer et al 2014[157]	Retrospective Cohort	323	Death Neurosurgery	✓		
35	Kim et al 2014[126]	Retrospective Cohort Subdurals only	98	Neurosurgery Progression CT	✓	✓	✓
36	Sweeney et al 2015[168]	Retrospective Cohort	50493	Neurosurgery	✓	✓	✓
37	Nishijima et al 2015[136]	Retrospective Cohort	151	Deterioration	✓		
38	Darby et al 2015[199]	Retrospective Cohort	369	Death Neurosurgery Progression CT	✓		✓
39	Beynon et al 2015[164]	Retrospective Cohort	70	Death Neurosurgery	✓		
40	Joseph et al 2015[27]	Retrospective Cohort	876	Neurosurgery Progression CT	✓	✓	✓
41	Ditty et al 2015[104]	Retrospective Cohort SAH/ICB only	500	Death Neurosurgery Progression CT	✓		
42	Anandalwar et al 2016[102]	Retrospective Cohort	142	Deterioration Neurosurgery	✓		
43	Bardes et al 2016[171]	Retrospective Cohort	389	Death Deterioration Neurosurgery Progression CT	✓	✓	✓
44	Shih et al 2016[170]	Retrospective Cohort	340	Deterioration Neurosurgery Progression CT	✓	✓	✓
45	Schwed et al 2016[144]	Retrospective Cohort	201	Deterioration Neurosurgery	✓	✓	✓
46	Sumritpradit et al 2016[147]	Retrospective Cohort	98	Deterioration Neurosurgery Progression CT	✓	✓	
47	Pruitt et al 2016[178]	Retrospective Cohort	1053	Deterioration Neurosurgery	✓		
48	Jospeph et al[31, 80, 81]	Three papers outlining the Brain Injury Guideline risk stratification tool and a combination of retrospective and prospective data following its implementation.					
49							
50							

Appendix 26: Table of Risk Factors Assessed

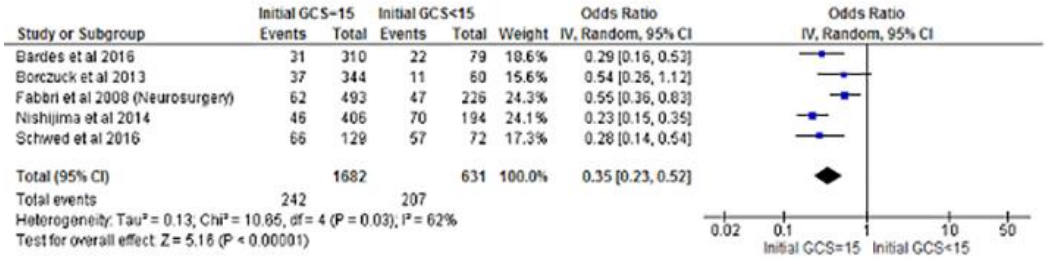
Risk Factor		Assessed Number of studies	Univariate	Multivariate	Recursive partitioning
1 Age	Continuous	10[84, 126, 140, 142, 144, 147, 148, 168-170, 199]	7[84, 126, 144, 147, 148, 169, 170, 199]	4[140, 142, 168, 199]	
	≥65	6[27, 109, 137, 145, 148, 149]	6[27, 109, 137, 145, 148, 149]	3[27, 145, 148]	1[137]
	≥60	1[113]	1[113]	1[113]	
	≥55	2[144, 171]	1[171]	1[144]	1[171]
	≥50	1[147]	1[147]		
2 Gender		10[27, 84, 109, 126, 140, 145, 147, 148, 168, 170]	9[27, 84, 109, 126, 145, 147, 148, 168, 170]	2[27, 140]	
3 Initial GCS	<15	7[109, 113, 137, 144, 145, 148, 171]	6[109, 113, 137, 144, 145, 171]	4[109, 144, 145, 148]	2[137, 171]
	GCS	7[84, 126, 140, 144, 148, 168, 170]	4[84, 126, 144, 148, 170]	2[140, 168]	
	GCS=14	1[84]		1[84]	
	GCS=13	1[84]		1[84]	
4 CT Findings	Midline shift CT/Mass effect	5[84, 126, 137, 147, 170]	4[84, 137, 147, 170]	4[84, 126, 147, 170]	1[137]
	Marshall Classification	2[113, 144]	2[113, 144]		
	SDH>10mm	1[27]	1[27]	1[27]	
	EDH>10mm	1[27]	1[27]	1[27]	
	ICH vol>10ml	1[149]	1[149]	1[149]	
	Mean Vol	1[126]	1[126]	1[126]	
	Maximal thickness	1[126]		1[126]	
	Volume ED	1[170]	1[170]	1[170]	
	Volume SDH	1[170]	1[170]		
	Volume ICB	1[170]	1[170]		
5 Type of isolated injury	Contusion	1[109, 149]	1[109, 149]		
	SDH	3[109, 144, 168]	2[109, 144]	1[168]	
	EDH	3[109, 144, 168]	2[109, 144]	1[168]	
	SAH	3[109, 144, 168]	2[109, 144]	2[144, 168]	
	Mixed	1[144, 168]	1[144]	1[168]	
	ICB	1[144]	1[144]		
6 Presence of (includes	Contusion	3[109, 147]	3[109, 147]		

mixed injuries)					
	SDH	**5**[84, 109, 147, 170, 171]	**5**[84, 109, 147, 170, 171]	**1**[109]	
	EDH	**5**[84, 109, 147, 170, 171]	**5**[84, 109, 147, 170, 171]		
	SAH	**4**[84, 109, 147, 170, 171]	**4**[84, 109, 147, 170, 171]		
	fracture	**4**[84, 145, 147, 170]	**4**[84, 145, 147, 170]	**1**[170]	
	Displaced/depressed fracture	**2**[27, 137]	**2**[27, 137]	**1**[27]	
	Base of skull fracture	**2**[**145, 147**]	**2**[145, 147]		
	pneumocranium	**1**[170]	**1**[170]		
	ICB	**3**[84, 170, 171]	**3**[84, 170, 171]		
	IVH	**3**[84, 147, 170]	**3**[84, 147, 170]		
	Diffuse Axonal Injury	**1**[147]	**1**[147]		
	2+ lesions	**4**[84, 145, 148, 170]	**4**[84, 145, 148, 170]	**2**[145, 148]	
	3+ lesions	**1**[84]	**1**[84]		
7 Subdural with	**contusion**	**1**[126]	**1**[126]	**1**[126]	
	SAH	**1**[126]	**1**[126]	**1**[126]	
8 Non-isolated head Injury		**1**[**137**]	**1**[**137**]		**1**[137]
9 BP		**7**[27, 144, 147, 148, 168-170]	**6**[27, 144, 147, 148, 169, 170]	**2**[144, 168]	
10 Pre-admission Hypotension		**1**[**137**]	**1**[**137**]		
11 HR		**4**[27, 144, 168, 169]	**3**[27, 144, 169]	**1**[168]	
12 RR		**1**[168]	**1**[168]		
13 Pre-injury Hypoxia		**1**[**137**]	**1**[**137**]		
14 Intoxication		**2**[27, 126]	**2**[27, 126]		
15 Coagulopathy : including any anti-coagulant use		**6**[84, 113, 126, 148, 168, 170]	**5**[84, 113, 126, 148, 170]	**1**[168]	
16 Warfarin Use		**3**[109, 147, 171]	**3**[109, 147, 171]		
20 Warfarin or anti-platelet		**2**[149, 170]	**2**[149, 170]		
17 PT/INR		**3**[84, 145, 171]	**3**[84, 145, 171]		
18 aPPT		**1**[84, 171]	**2**[84, 171]		
19 Platelet count<100000		**1**[27]	**1**[27]	**1**[27]	
20 Platelet count<50000		**1**[126]	**1**[126]		
21 Hb<10		**1**[27]	**1**[27]		
22 Hb		**2**[145, 170]	**2**[145, 170]		
23 WCC		**1**[170]	**1**[170]	**1**[170]	
24 Aspirin		**3**[109, 147, 171]	**3**[109, 147, 171]		
25 Clopidogrel		**3**[109, 147, 171]	**3**[109, 147, 171]		
25 Any Anti-platelet		**2**[126, 137, 158]	**1**[126, 137]	**1**[158]	

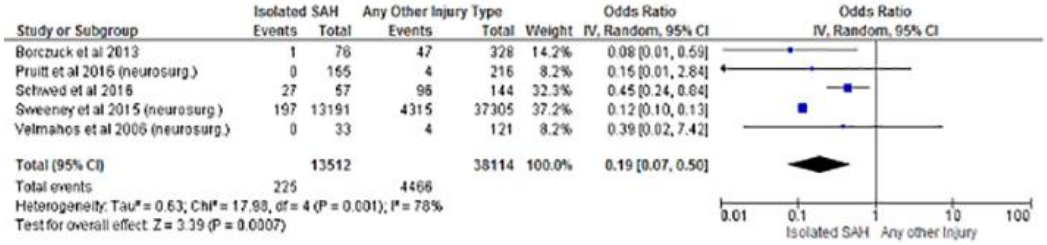
26 ISS		**11**[84, 140, 142, 144, 147, 148, 168-171, 199]	**9**[84, 113, 144, 147, 148, 169-171, 199]	**7**[84, 140, 142, 144, 168, 170, 199]	
27 (H)AIS		**5**[113, 144, 147, 169, 171]	**5**[113, 144, 147, 169, 171]	**1**[144]	
28 LOC		**1**[27]	**1**[27]	**1**[27]	
29 Mechanism of Injury (unqualified)		**2**[27, 126]	**2**[27, 126]		
30 Non-fall from standing		**1**[137]	**1**[137]		
31 Fall		**2**[109, 148]	**2**[109, 148]		
32 Assault		**1**[109]	**1**[109]		
33 RTC		**4**[109, 145, 147, 148]	**4**[109, 145, 147, 148]		
34 Pedestrian Struck		**1**[109]	**1**[109]		
35 Bicycle struck		**1**[109]	**1**[109]		
36 Lactate		**1**[27]	**1**[27]	**1**[27]	
37 Base deficit		**1**[27]	**1**[27]	**1**[27]	
38 Comorbidities	**HTN**	**3**[109, 147, 170]	**3**[109, 147, 170]		
	Diabetes	**2**[147, 170]	**2**[147, 170]		
	Old CVA	**2**[147, 170]	**2**[147, 170]		
	IHD	**2**[147, 170]	**2**[147, 170]		
	Arrhythmia	**1**[170]	**1**[170]		
	Liver disease	**1**[170]	**1**[170]		
	CKD	**1**[170]	**1**[170]		
	AKI	**1**[170]	**1**[170]		
	Any high risk	**1**[137]	**1**[137]		
39 Smoking		**1**[126]	**1**[126]		
40 Time to first CT		**2**[144, 147]	**2**[144, 147]		
41 Statin Therapy		**1**[170]	**1**[170]		

Appendix 27: Forest plots of within study risk factors' effect on the risk of neurosurgery or clinical deterioration

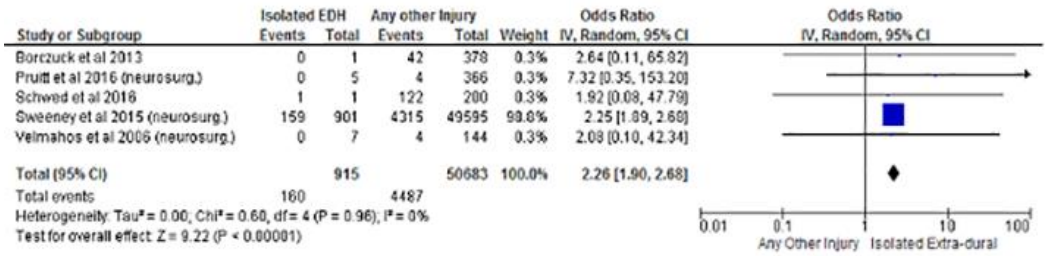
Meta-analysis of effect of initial GCS = 15 on risk of clinical deterioration/neurosurgery



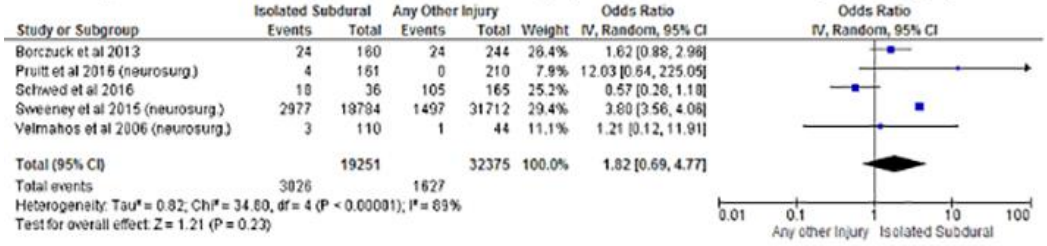
Meta-analysis effect of isolated subarachnoid hemorrhage vs. any other injury on clinical deterioration/neurosurgery



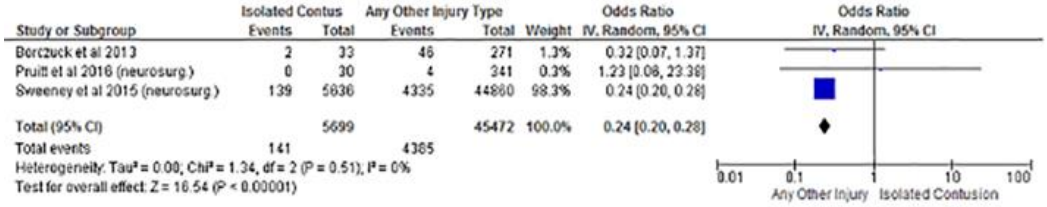
Meta-analysis effect of isolated extra-dural vs. any other injury on clinical deterioration/neurosurgery



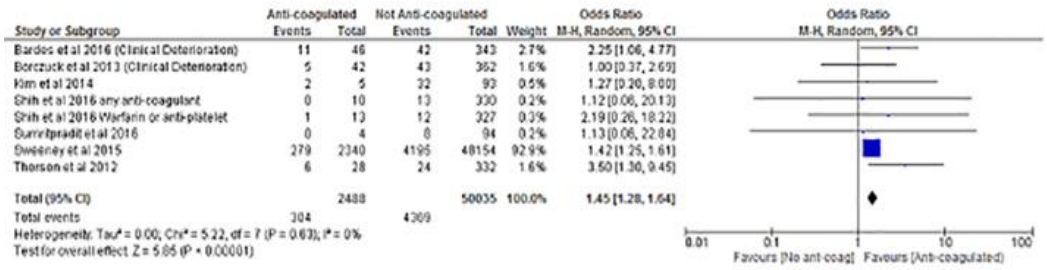
Meta-analysis effect of isolated subdural vs. any other injury on clinical deterioration/neurosurgery



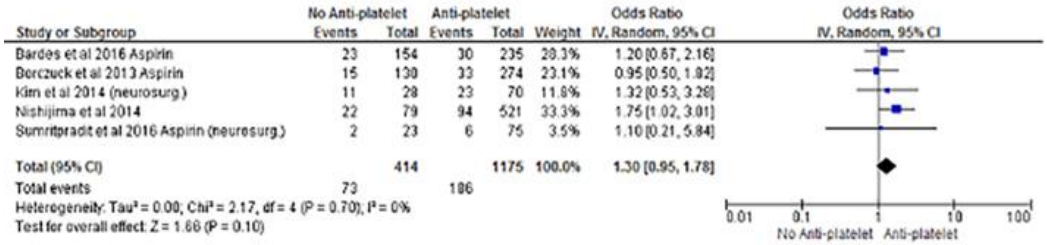
Meta-analysis effect of isolated contusion vs. any other injury on clinical deterioration/neurosurgery



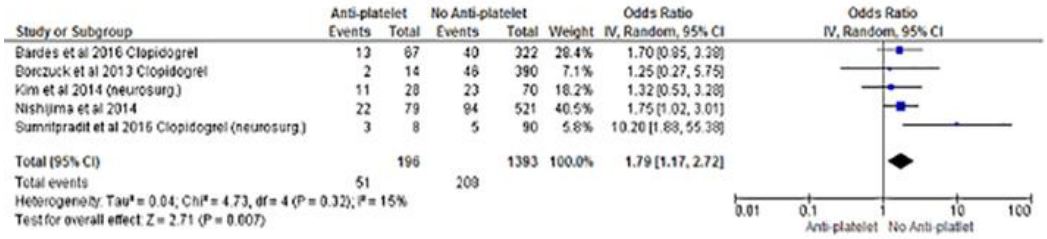
Meta-analysis of effect of coagulopathy use on clinical deterioration/neurosurgery



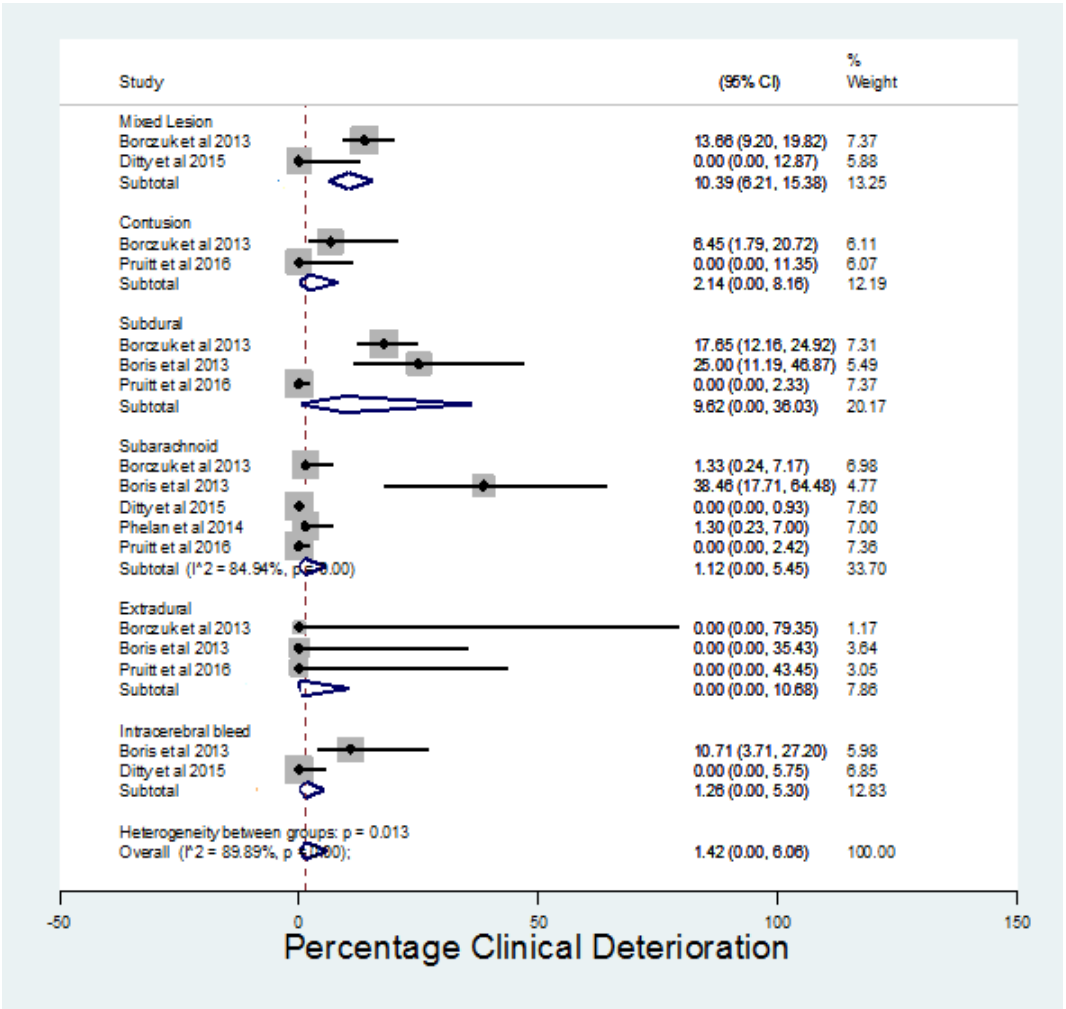
Meta-analysis of effect of aspirin/anti-platelet use on clinical deterioration/neurosurgery



Meta-analysis effect of clopidogrel/anti-platelet use on clinical deterioration/ neurosurgery



Appendix 28: Pooled risk of clinical deterioration stratified by the injury type identified by initial CT imaging



Appendix 29: The Brain Injury Guideline (BIG) criteria:

	BIG1 (Discharge from ED after 6 hours)	BIG2 (Non-specialist hospital admission)	BIG3* (Specialist hospital admission)
Neurological Examination	GCS13-15 Normal pupils No Focal Neurological deficit	GCS13-15 Normal pupils No Focal Neurological deficit	GCS<13 Or Abnormal pupils Or Focal Neurological deficit
Intoxicated	No	No/Yes	No/Yes
Anticoagulants or Anti-platelets	No	No	Yes
Skull Fracture	No	Non-displaced	Displaced
Intracranial Bleed	Subdural Haemorrhage <5mm Or Extradural Haemorrhage <5mm Or 1 Intraparenchymal Haemorrhage <5mm Or Trace Subarachnoid Haemorrhage	Subdural Haemorrhage 5-7mm Or Extradural Haemorrhage 5-7mm Or 1-2 Intraparenchymal Haemorrhages 5-7mm Or Localised Subarachnoid Haemorrhage	All other injuries
Intra-ventricular Haemorrhage	No	No	Yes

*Patients must fulfil all the criteria of BIG1 or BIG2 to be categorised as such and are otherwise automatically in BIG3

Appendix 30: Categorisation of TBI severity

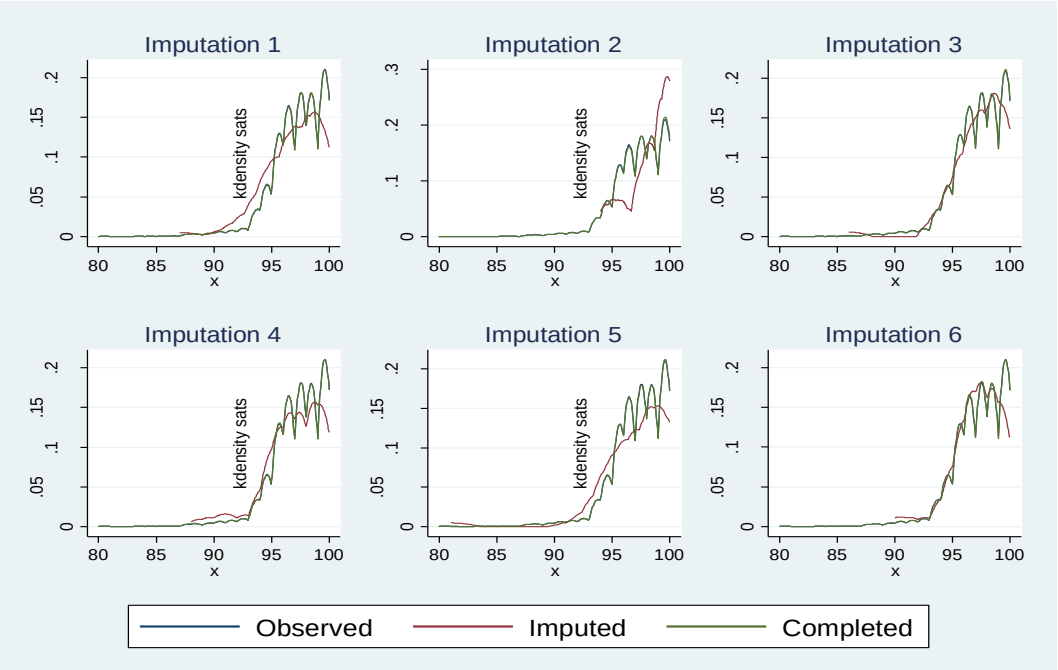
Category	Injury Description written CT report	AIS Codes	Equivalent Marshal Classification (Lesko et at[11])
1	Vault skull fractures	150000, 150400 150402	
2	Basal, depressed, open skull fractures	150200, 150204, 150205, 150206, 150404, 150406, 150408	I
3	1-2 Bleeds* /contusions total diameter <5mm	140605, 140631, 140639, 140651, 140693, 140694 (and written CT report indicated injury <5mm)	
4	Bleed/contusion No or minor mass effect	140602,140604,140606,140612,140614,140611,140620, 140622, 140628,140629,140630,140632,140634,140638,140640, 140642, 140644,140646,140650,140652,140654,140684,140688, 140686, 140699, 140676, 140678, 140680, 140682, 140799	II
5**	Bleed/contusion Significant midline shift or mass effect indicated in CT report	140202, 140660, 140662, 140664, 140666	III/IV
6		140608,140610,140616,140618,140624,140626,140636, 140648, 140656, 140637, 140655	VI
7	Cerebellar/brainstem injury	140204,140206,140208,140210,140212,140214,140218, 140299, 140402,140403,140404,140405,140406,140410,140414, 140418, 140422,140426,140430,140434,140438,140442,140446, 140450, 140458,140462,140466,140470,140474,140499,	VII

*Bleeds refers to subdural, extradural, intracerebral and subarachnoid haemorrhage

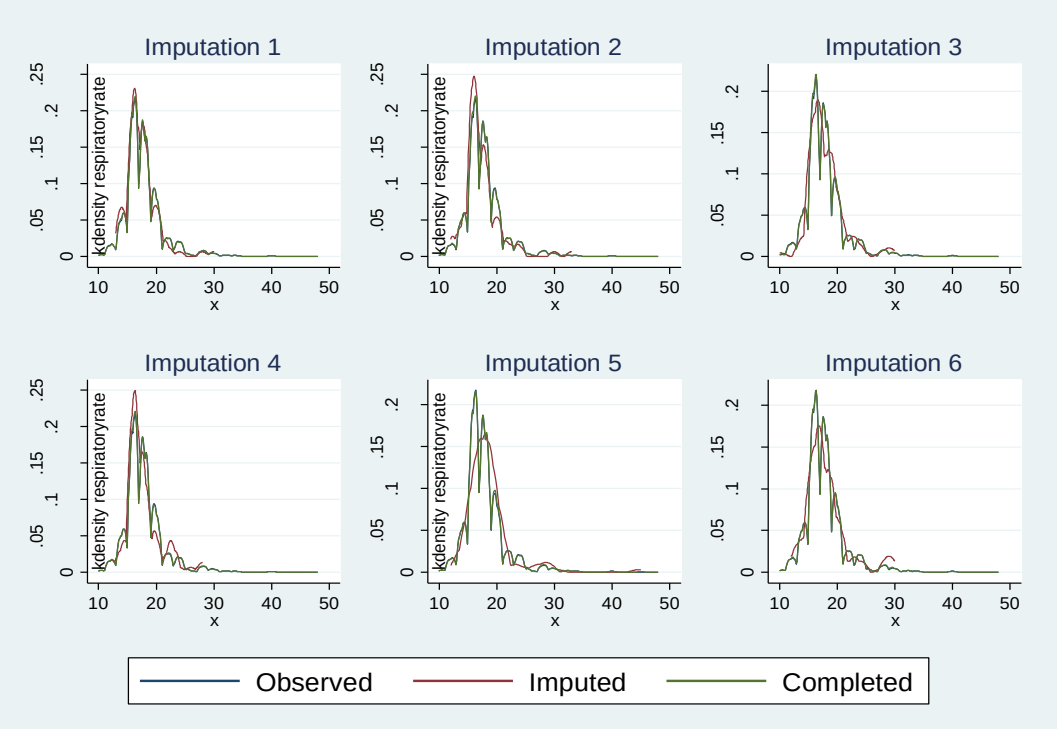
**Written CT reports did not allow easy differentiation in the extent of mass effect, and therefore Marshall III and IV categories were collapsed into 1 category.

Appendix 31: Distribution of observed and imputed data of first 6 imputations of 25:

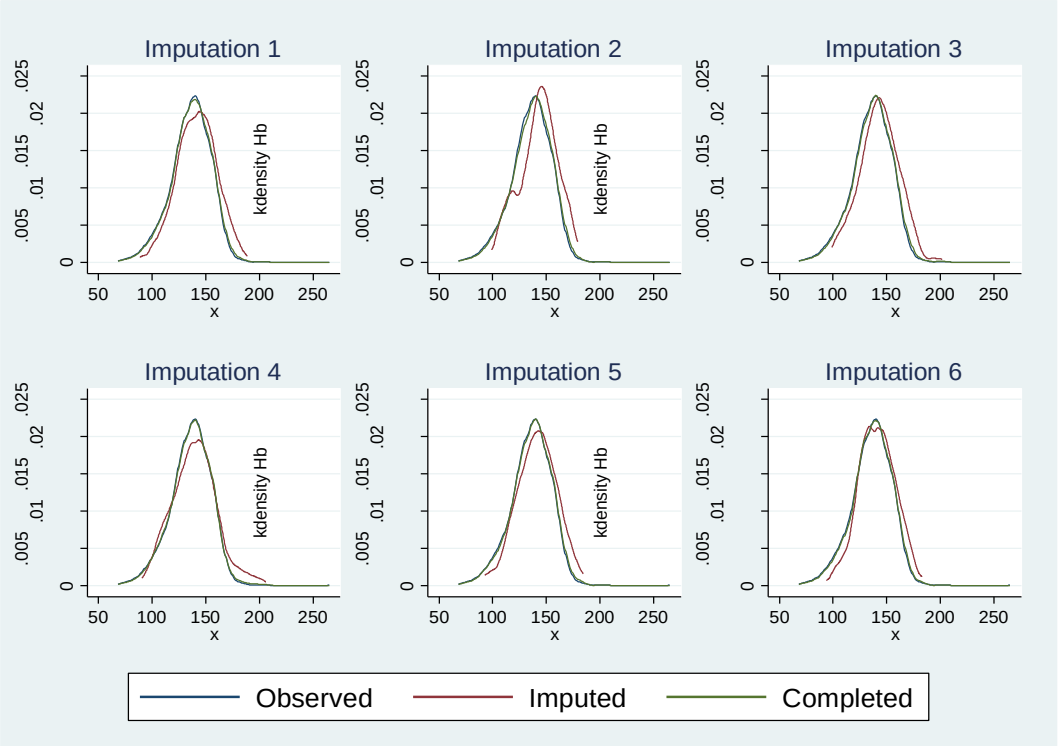
Saturations:



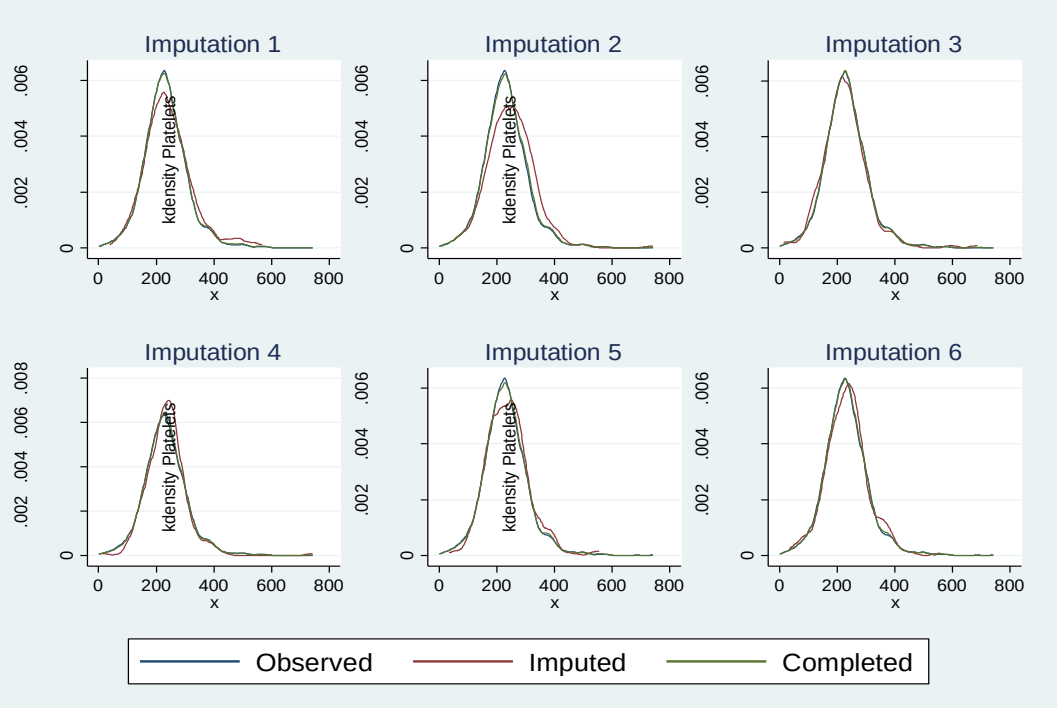
Respiratory Rate:



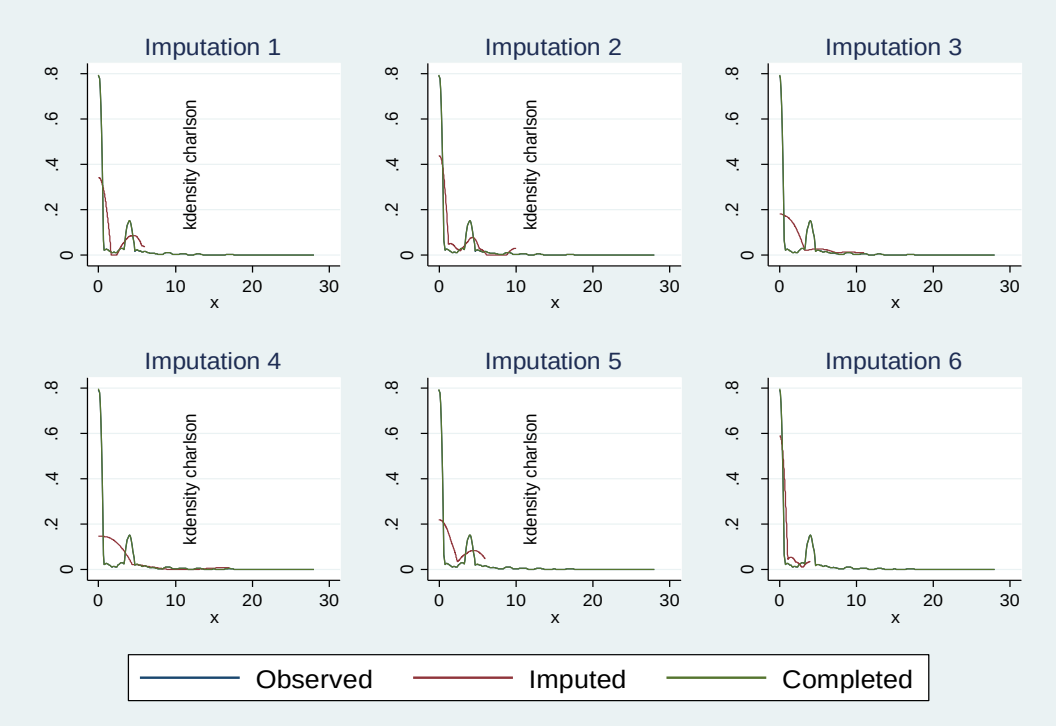
Hb:



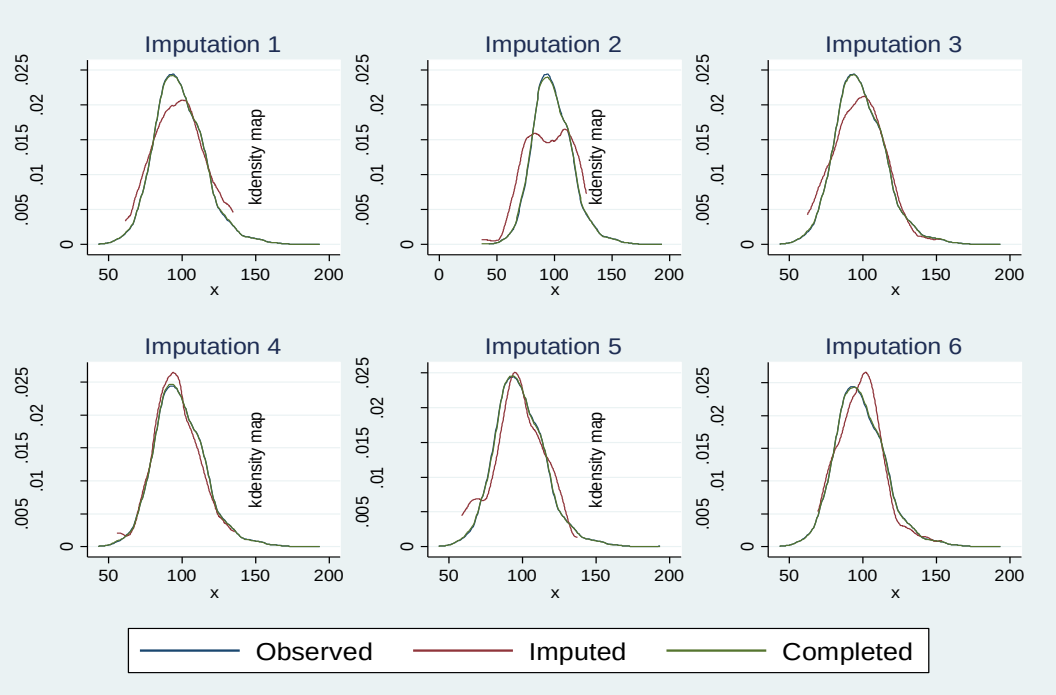
Platelets:



Charlson Score:



MAP:



298

Intoxication:

	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	29.7%	29.7%	29.7%	29.7%	29.7%	29.7%
Imputed	42.1%	34.2%	34.2%	39.5%	47.4%	36.8%
Completed	30%	29.8%	29.8%	30%	30.1%	29.9%

Prehospital or ED Seizure:

	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	4.4%	4.4%	4.4%	4.4%	4.4%	4.4%
Imputed	0%	22.3%	0%	11.1%	0%	11.1%
Completed	4.4%	4.5%	4.4%	4.4%	4.4%	4.4%

Prehospital or ED Vomiting:

	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	18.4%	18.4%	18.4%	18.4%	18.4%	18.4%
Imputed	8.3%	16.7%	16.7%	16.7%	33.3%	25%
Completed	18.3%	18.4%	18.4%	18.4%	18.5%	18.4%

GCS:

GCS:15	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	57.6%	57.6%	57.6%	57.6%	57.6%	57.6%
Imputed	60%	40%	60%	60%	80%	40%
Completed	57.6%	57.6%	57.6%	57.6%	57.6%	57.6%
GCS:14	Imputation 4	Imputation 2	Imputation 4	Imputation 4	Imputation 5	Imputation 6
Observed	31.5%	31.5%	31.5%	31.5%	31.5%	31.5%
Imputed	40%	40%	40%	40%	20%	60%
Completed	31.5%	31.5%	31.5%	31.5%	31.5%	31.5%
GCS:13	Imputation 4	Imputation 2	Imputation 4	Imputation 4	Imputation 5	Imputation 6
Observed	10.9%	10.9%	10.9%	10.9%	10.9%	10.9%
Imputed	0%	20%	0%	0%	0%	0%
Completed	10.9%	10.9%	10.9%	10.0%	10.9%	10.0%

Abnormal First Neurological Examination:

	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	14.5%	14.5%	14.5%	14.5%	14.5%	14.5%
Imputed	14.6%	30.3%	21.3%	21.3%	19.1%	13.5%
Completed	14.5%	15.3%	14.8%	14.8%	14.7%	14.4%

Frailty (no missing data under 50 category):

Under 50	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	38.8%	38.8%	38.8%	38.8%	38.8%	38.8%
Imputed	10.7%	7.1%	7.1%	7.1%	10.7%	10.7%
Completed	38.4%	38.3%	38.3%	38.3%	38.4%	38.4%
CFS 1-3	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	38.4%	38.4%	38.4%	38.4%	38.4%	38.4%
Imputed	64.3%	75%	75%	75%	67.9%	64.3%
Completed	38.8%	39%	39%	39%	38.9%	38.8%
CFS 3-6	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	18.4%	18.4%	18.4%	18.4%	18.4%	18.4%
Imputed	17.9%	14.3%	14.3%	17.9%	17.9%	17.9%
Completed	18.4%	18.4%	18.4%	18.4%	18.4%	18.4%
CFS 7-9	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	Imputation 6
Observed	4.3%	4.3%	4.3%	4.3%	4.3%	4.3%
Imputed	7.1%	3.6%	3.6%	0%	3.6%	7.1%
Completed	4.4%	4.3%	4.3%	4.2%	4.3%	4.4%

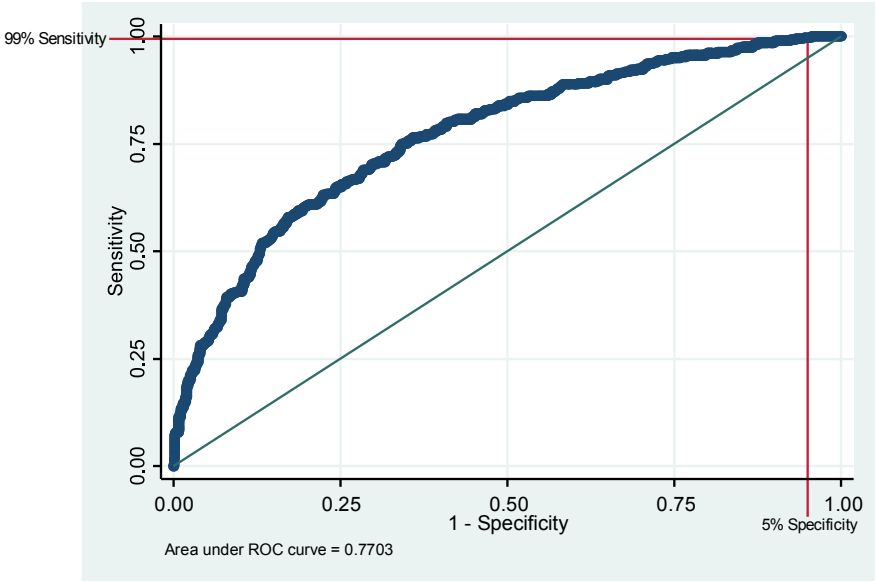
Appendix 32: Multivariable Models selected in complete case analysis

Candidate Factor	Category	Multivariable effect on risk of deterioration: Odds Ratio (95% CI)	Multivariable effect on risk of deterioration: Odds Ratio (95% CI)
Age	Year (1 unit increase)	*	$(Age/10)^3$ Fractional Polynomial 0.997 (0.996 to 0.999
GCS Vs 15	GCS14 GCS13	1.5 (1.1 to 2.1) 2.7 (1.8 to 4.1)	1.6 (1 to 2.5) 4.2 (2.4 to 7.2)
Abnormal Neurological Examination	Abnormal	1.4 (0.99 to 2.1)	2.1 (1.3 to 3.5)
Injury severity on CT Vs simple skull fracture (categories described in detail supplementary material 2)	2) Complex Skull fractures 3)1-2 bleeds < 5mm (total) 4) No or minimal mass effect 5) Significant midline shift 6) High/mixed-density lesion 7) Cerebellar/Brain stem injury	1.3 (0.4 to 4.5) 0.7 (0.2 to 2.2) 1.8 (0.6 to 5.4) 5.6 (1.8 to 17.5) 14.4 (4.4 to 46.6) 10.1 (2 to 49.8)	1.3 (0.2 to 7.2) 0.6 (0.1 to 3.6) 2.3 (0.5 to 10.2) 11 (2.3 to 52) 47.4 (9.9 to 227.5) 10.5 (1.2 to 89.3)
Subdural bleed	Yes	1.8 (1.3 to 2.4)	*
Extracranial Injury	ISS (1 unit increase)	*	1.06 (1.03 to 1.1)
Rockwood Frailty Score Vs under 50	CFS 1-3 CFS 4-6 CFS 7-9	*	1.4 (0.8 to 2.6) 0.6 (0.2 to 1.7) 0.1 (0.01 to 1.05)
Preinjury Anti-coagulation or anti-platelets	Yes	1.3 (1 to 1.8)	*
Intoxicated	Yes	*	0.6 (0.4 to 0.95)
Number of Injuries on CT Vs 1	2 3 4 5 Diffuse injury	*	0.9 (0.5 to 1.5) 0.7 (0.4 to 1.4) 1.6 (0.8 to 3.1) 2.5 (1.2 to 5.1) 2.1 (0.2 to 18.4)
Contusion Present	Yes	1.3 (0.99 to 1.8)	*
Extradural bleed	Yes	1.7 (1 to 2.8)	*
Intraparenchymal haemorrhage Present	Yes	*	0.5 (0.2 to 0.9)
Intra-ventricular bleed	Yes	1.9 (0.9 to 3.9)	*

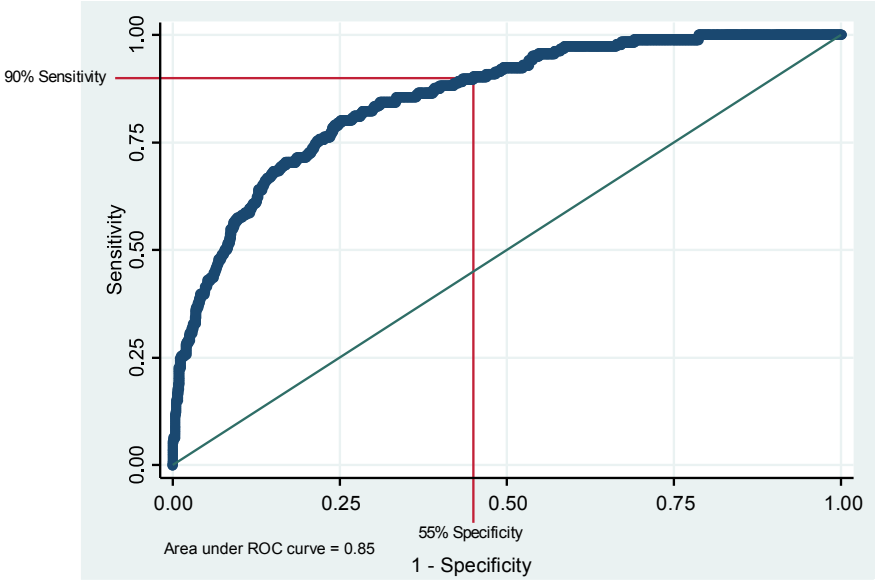
*Not Selected into model

Appendix 33: ROC curves of model performance

a) ROC curve of derived model for primary composite outcome of deterioration for discharge from the ED



b) ROC curve of derived model for secondary composite outcome of deterioration indicating need for specialist neurosurgical admission



*AUC estimated in patients with complete data for explanatory variables in each model

Appendix 34: Performance of risk score including Hb

Factor	**Coefficient (optimism adjusted)**	**Risk Score Value**
Preinjury Anti-coagulation or anti-platelets	0.3	1
GCS 15 14 13	 0 (Vs) 0.4 0.7	 **GCS 15** 0 **GCS 14** 1 **GCS 13** 2
Normal first Neurological Examination	0.45	**Abnormal** 1.5
Number of Injuries on CT **1** **2** **3** **4** **5** **Diffuse**	 0 (Vs) 0.25 0.4 0.8 0.9 0.3	 **1** 0 **2** 1 **3** 1 **4** 3 **5** 3 **Diffuse** 1
Injury severity on CT* **1** simple skull fracture **2** complex Skull Fracture **3** 1-2 bleeds < 5mm **4** Marshall II **5** Marshall II/IV **6** Marshall VI **7** Brain stem/Cerebellar	 0 (Vs) 0.3 0.08 0.7 1.7 2.7 1.7	 **1** 0 **2** 1 **3** 0 **4** 2 **5** 5 **6** 9 **7** 5
ISS (body regions excluding head)	0.2	**Up to 2 non-significant extra-cranial injuries**** 0 **Any significant extra-cranial injury or 3 or more injuries** 2
Hb	-0.01	**Hb<10** 2
Constant	-1.38	

N=1370	**Deteriorated**	**Didn't deteriorate**	**Positive Predictive Value (PPV)** **Negative Predictive Value (NPV)**
Performance of Risk score			
Admission (Score>0)	396	912	PPV=30.3%
Discharge (Score=<u>≤</u>0)	2	60	NPV=96.8%
	Sensitivity = 99.5% (95% CI: 98% to 99.9%)	Specificity= 6.2% (95% CI: 4.8% to 7.9%)	

Appendix 35: risk stratification by risk score

Risk Score	**0**	**1-5**	**>5**
Deteriorated	2	181	242
Did not deteriorate	85	855	204
Prevalence deterioration	2.3%	15.5%	54%

Appendix 36: Sensitivity analysis the impact of the NICE head injury guidelines on monthly TBI mortality rate per 100 000 population (period of ICD9 coding prior to Jan 2001 removed)

Age Band	Winter Effect	Initial Trend	1st NICE Guideline	2nd NICE Guideline	3rd NICE Guideline
65+	-0.1 (95% CI: -0.2 to -0.06) P<0.01	0.009 (95% CI:- 0.002 to 0.02) P=0.1	**Change level:** -0.08 (95% CI:-0.3 to 0.14) P=0.5 **Change trend:** -0.002 (95% CI:-0.01 to 0.01) P=0.8	**Change level:** -0.1 (95% CI: -0.27 to 0.07) P=0.26 **Change trend:** 0.0004 (95% CI: -0.005 to 0.006) P=0.88	**Change level:** 0.14 (95% CI:-0.04 to 0.33) P=0.14 **Change trend:** -0.005 (95% CI:-0.01 to 0.002) P=0.15
16-64	-0.1 (95% CI: -0.14 to -0.07) P<0.01	0.0002 (95% CI:-0.01 to 0.005) P=0.93	**Change level:** 0.02 (95% CI: -0.09 to 0.13) P=0.76 **Change trend:** 0.003 (95% CI: -0.003 to 0.01) P=0.38	**Change level:** -0.06 (95% CI:-0.15 to 0.003) P=0.17 **Change trend:** *-0.005* *(95% CI:-0.007 to -0.002)* *P<0.01*	**Change level:** 0.005 (95% CI:-0.087 to 0.096) P=0.92 **Change trend:** 0.002 (95% CI:-0.002 to 0.005) P=0.37
0-15	-0.01 (95% CI:-0.01 to -0.003) P=0.02	-0.0006 (95% CI: -0.001 to 0.0002) P=0.12	**Change level:** 0.008 (95% CI: -0.01 to 0.02) P= 0.35 **Change trend:** 0.0004 (95% CI:-0.0005 to 0.001) P=0.37	**Change level:** -0.002 (95% CI: -0.01 to 0.01) P=0.76 **Change trend** 0.001 (95% CI:-0.0003 to 0.0005) P=0.58	**Change level:** -0.01 (95% CI:-0.03 to 0.002) P=0.1 **Change trend:** 0.0005 (95% CI: -0.00006 to 0.001) P=0.08

Appendix 37: Sample Collection Form

Start of Block: Default Question Block

Q1 Study number?

_____

Q2 How old was the patient when they attended the ED?

_____

Q3 Patient's sex?

- Male (1)
- Female (2)
- Unknown (3)

Q4 Pre-injury anti-coagulant use?

- Yes (1)
- No (2)
- Unknown (3)

Display This Question:

If Pre-injury anti-coagulant use? = Yes

Q5 Which anti-coagulant?

- [ ] Warfarin (1)
- [ ] LMWH (2)
- [ ] Apixaban (3)
- [ ] Dabigatran (4)
- [ ] Rivaroxaban (5)
- [ ] Fondaparinux (6)

Q6 Pre-injury anti-platelet use?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Display This Question:

If Pre-injury anti-platelet use? = Yes

Q7 Which anti-platelet?

- [ ] Aspirin (1)
- [ ] Clopidogrel (2)
- [ ] Dipyridamole (3)
- [ ] Ticagrelor (4)
- [ ] Ticlopidine (5)
- [ ] Tirofiban (6)
- [ ] Unknown (7)

*

Q8 Date of injury?

_____

Q9 Time of injury?

- ○ Unknown (1)
- ○ Known (2)

Display This Question:

If Time of injury? = Known

Q10 Time of Injury? (in 24 hour clock)

_____

Q11 Was the mechanism of injury a pedestrian or cyclist struck by a motor vehicle?

- Yes (1)
- No (2)
- Unknown (3)

Q12 Was the mechanism of injury an occupant ejected from a motor vehicle?

- Yes (1)
- No (2)
- Unknown (3)

Q13 Was the mechanism of injury a fall from a height greater than 1 meter or 5 stairs?

- Yes (1)
- No (2)
- Unknown (3)

Q14 Mechanism of injury?

- ○ Fall (1)
- ○ Assault (2)
- ○ Road traffic collision (3)
- ○ Sport (4)
- ○ Other (6)
- ○ Unknown (7)

Q15 Post-traumatic amnesia?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown/Patient unable to give a clinical history (3)

Display This Question:

If Post-traumatic amnesia? = Yes

Q16 Was amnesia?

- ○ Anterograde (1)
- ○ Retrograde (2)
- ○ Both (3)

Display This Question:
If Was amnesia? = Anterograde

Q17 Duration of anterograde amnesia?

- ○ Greater than 30 mins (1)
- ○ Less then 30 mins (2)
- ○ Unknown (3)

Display This Question:
If Was amnesia? = Retrograde

Q18 Duration of retrograde amnesia?

- ○ Greater than 30 mins (1)
- ○ Less than 30 mins (2)
- ○ Unknown (3)

Q19 Intoxicated at time of injury?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Q20 Seizures before arrival to ED?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Display This Question:

If Seizures before arrival to ED? = Yes

Q21 Number of seizures

_____

Q22 Vomiting before arrival to ED?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Display This Question:

If Vomiting before arrival to ED? = Yes

Q23 Number of vomits?

_____

Q24 Date of arrival ED?

_____

Q25 Time of arrival ED? (24 hour clock)

_____

Q26 GCS formally documented in ED?

- Yes (1)
- No (2)

Display This Question:

If GCS formally documented in ED? = Yes

Q27 First recorded GCS score in the ED?

_____

Display This Question:

If GCS formally documented in ED? = No

Q28 Can conclude from ED record GCS 15 on initial assessment? (alert and giving a clear history of events)

- ○ Yes (1)
- ○ No (3)

Q29 BP recorded in ED?

- ○ Yes (1)
- ○ No (3)

Display This Question:

If BP recorded in ED? = Yes

*

Q30 First recorded systolic BP in the ED?

_____

Display This Question:

If BP recorded in ED? = Yes

*

Q31 First recorded diastolic BP in the ED?

_____

Q32 Oxygen saturation recorded in ED?

- ○ Yes (1)
- ○ No (3)

Display This Question:

If Oxygen saturation recorded in ED? = Yes

Q33 First recorded oxygen saturation in the ED?

_____

Q34 Respiratory rate recorded in ED?

- ○ Yes (1)
- ○ No (3)

Display This Question:

If Respiratory rate recorded in ED? = Yes

Q35 First recorded respiratory rate in the ED?

_____

Q36 Normal first neurological examination in ED? (excluding pupillary response)

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Q37 Equal pupils first examination?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Q38 Both pupils reactive first examination?

- ○ Yes (1)
- ○ Unknown (2)
- ○ No (3)

Q39 Signs of a skull fracture first examination?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Display This Question:

If Signs of a skull fracture first examination? = Yes

Q40 Sign of skull fracture?

- ☐ CSF leak (1)
- ☐ Haemotympanum (2)
- ☐ Battle sign (bruising behind ear) (3)
- ☐ Panda eyes (peri-orbital bruising) (4)
- ☐ Boggy swelling or other evidence of a open/depressed skull fracture (5)
- ☐ Obvious open skull fracture (6)

Q41 Documented seizures in the ED?

- Yes (1)
- No (3)
- Incomplete notes (2)

Display This Question:

If Documented seizures in the ED? = Yes

Q42 Number of seizures?

_____

Q43 Documented vomiting in the ED?

- Yes (1)
- No (2)
- Incomplete notes (3)

Display This Question:

If Documented vomiting in the ED? = Yes

Q44 Number of vomits?

_____

Q45 Any Co-morbidities?

- ○ Yes (1)
- ○ No (2)
- ○ Unknown (3)

Display This Question:

If Any Co-morbidities? = Yes

Q46 Any of the following co-morbidities? (documented up to 1 year previously in the notes)

- [ ] Acute myocardial infarction (1)
- [ ] Cerebral vascular accident (2)
- [ ] Congestive heart failure (3)
- [ ] Connective tissue disease (4)
- [ ] Dementia (5)
- [ ] Liver disease (6)
- [ ] Gentito-urinary disease (7)
- [ ] Peptic ulcer (8)
- [ ] Peripheral vascular disease (9)
- [ ] Pulmonary disease (10)
- [ ] Cancer (11)
- [ ] Paraplegia (12)
- [ ] Renal Disease (13)
- [ ] Metastatic cancer (14)

☐ HIV (15)

☐ Mental health (16)

☐ Blood disease (17)

☐ Bone disease (18)

☐ Neurological disorders (19)

☐ Alcohol abuse (20)

☐ Diabetes (21)

Display This Question:

If If How old was the patient when they attended the ED? Text Response Is Greater Than or Equal to 50

*

Q47 What is their clinical frailty scale score? (1-9 check here http://camapcanada.ca/Frailtyscale.pdf)

_____

Q48 Copy initial CT report (written report, whole)

_____

Q50 Single brain injury or skull fracture on initial CT?

- Yes (1)
- No (2)

Display This Question:

If Single brain injury or skull fracture on initial CT? = No

Q98 Number of injuries to skull and brain?

- 2 (1)
- 3 (2)
- 4 (3)
- 5 (4)
- Multiple diffuse injuries- single injury code (5)

Display This Question:

If Single brain injury or skull fracture on initial CT? = Yes

Q51 Type of single injury?

- ○ Subdural haemorrhage (1)
- ○ Extra-dural haemorrhage (2)
- ○ Intra-cerebral haemorrhage (3)
- ○ Subarachnoid haemorrhage (4)
- ○ Brain contusion (5)
- ○ Vault skull fracture (6)
- ○ Basal skull fracture (7)

Display This Question:

If Single brain injury or skull fracture on initial CT? = Yes

*

Q100 Injury Code of single injury?

_____

Display This Question:

If Number of injuries to skull and brain? = 2

*

Q103 Injury Code of 1st of 2 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 2

Q104 Injury Code 2nd of 2 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 3

Q105 Injury Code 1st of 3 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 3

Q106 Injury Code 2nd of 3 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 3

Q107 Injury Code 3rd of 3 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 4

Q108 Injury Code 1st of 4 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 4

*

Q109 Injury code 2nd of 4 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 4

*

Q111 Injury Code 3rd of 4 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 4

*

Q112 Injury code 4 of 4 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 5

*

Q113 Injury code 1st of 5 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 5

Q114 Injury code 2nd of 5 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 5

Q115 Injury code 3rd of 5 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 5

Q116 Injury code 4th of 5 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = 5

Q117 Injury code 5 of 5 injuries?

_____

Display This Question:

If Number of injuries to skull and brain? = Multiple diffuse injuries- single injury code

Q118 Injury code for diffuse Injury?

_____

Q52 Comment on the presence of midline shift or mass effect in the CT report?

- Yes (1)
- No (2)

Q53 Comment on the size of largest intra-cranial injury in CT report?

- Yes (2)
- No (1)

Q95 Indication in report size of injury less than 5mm (e.g. tiny or v. small)?

- Yes (1)
- No (2)

Display This Question:

If Comment on the size of largest intra-cranial injury in CT report? = Yes

Q54 Size of bleed or contusion in mm?

_____

Q55 Admission Hb available?

- Yes (1)
- No (2)

Display This Question:

If Admission Hb available? = Yes

Q56 Hb Value in grams per deci-litre?

_____

Q57 Admission platelets available?

- Yes (1)
- No (2)

Display This Question:

If Admission platelets available? = Yes

Q58 Admission platelets value (grams per liter)

_____

Q59 BM documented in ED?

- Yes (1)
- No (2)

Display This Question:

If BM documented in ED? = Yes

Q60 Value of first BM in ED?

_____

Q61 Extra-cranial injuries?

- Yes (1)
- No (2)
- Unknown (3)

Display This Question:

If Extra-cranial injuries? = Yes

Q62 Body region extra-cranial injuries? (as identified radiologically or on post-mortem)

- [ ] Thorax (1)
- [ ] Abdomen (2)
- [ ] Lower Limbs/Pelvis (4)
- [ ] Upper Limbs (5)
- [ ] Neck (6)
- [ ] C-Spine (7)
- [ ] Face (8)
- [ ] Thoracic Spine (9)
- [ ] Lumbar Spine (10)

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Neck

Q89 Abbreviated Injury score neck?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Thorax

Q63 Abbreviated injury score thorax?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Abdomen

Q64 Abbreviated injury score abdomen?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Lower Limbs/Pelvis

Q66 Abbreviated injury score lower limbs/pelvis?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = C-Spine

Q94 Abbreviated injury score C-spine?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Thoracic Spine

Q96 Abbreviated injury score Thoracic-spine?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Lumbar Spine

Q97 Abbreviated injury score Lumbar-spine?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Face

Q93 Abbreviated injury score face?

_____

Display This Question:

If Body region extra-cranial injuries? (as identified radiologically or on post-mortem) = Upper Limbs

Q67 Abbreviated injury score upper limbs?

_____

Q68 Death documented within 30 days of ED attendance within patient record?

- Yes (1)
- No (2)

Display This Question:

If Death documented within 30 days of ED attendance within patient record? = Yes

Q69 Cause of death recorded as due to traumatic brain injury?

- Yes (1)
- No (2)
- Unknown (3)

Display This Question:

If Cause of death recorded as due to traumatic brain injury? = Yes

Q70 Cause of death direct result of TBI or due to a complication (e.g. aspiration pneumonia)?

- Direct cause (1)
- Indirect cause (2)

Display This Question:

If Death documented within 30 days of ED attendance within patient record? = Yes

Q71 Was death within 24 hours of ED attendance?

- yes (1)
- No (2)

Q72 First neurosurgical procedure documented within 30 days of ED attendance (excludes spinal surgery)?

- Yes (1)
- No (2)

Display This Question:

If First neurosurgical procedure documented within 30 days of ED attendance (excludes spinal surgery)? = Yes

Q73 Neurosurgical procedure?

- Craniotomy (1)
- Intra-cranial bolt (2)
- Burr hole (3)
- Other (4)

Display This Question:

If First neurosurgical procedure documented within 30 days of ED attendance (excludes spinal surgery)? = Yes

Q74 Date of neurosurgical procedure?

_____

Q75 Did the patient have a documented seizure up to 30 days following inpatient admission from the ED?

- Yes (1)
- No (2)

Display This Question:

If Did the patient have a documented seizure up to 30 days following inpatient admission from the ED? = Yes

Q76 First seizure occurred?

- Within 24 hours of admission from the ED (1)
- After 24 hours of admission from the ED (2)

Q77 Documented drop in GCS score of 2 or more points from initial GCS score up to 30 days following ED attendance?

- Yes (1)
- No (2)

Display This Question:

If Documented drop in GCS score of 2 or more points from initial GCS score up to 30 days following E... = Yes

Q78 Drop in GCS by 2 or more points occurred?

- ○ Within 24 hours of ED attendance (1)
- ○ After 24 hours of ED attendance (2)

Q90 Was the patient admitted to intensive care within 30 days of ED attendance?

- ○ Yes (1)
- ○ No (2)

Display This Question:
If Was the patient admitted to intensive care within 30 days of ED attendance? = Yes

Q91 Was ICU admission within 24 hours of ED attendance?

- ○ Yes (1)
- ○ No (3)

Display This Question:
If Was the patient admitted to intensive care within 30 days of ED attendance? = Yes

Q92 Was ICU admission primarily for brain injury?

- ○ Yes (1)
- ○ No (3)

Q79 Patient intubated up to 30 days following ED attendance?

- ○ Yes (1)
- ○ No (2)

Display This Question:
If Patient intubated up to 30 days following ED attendance? = Yes

Q80 Did Intubation occur?

- ○ Within 24 hours of ED attendance (1)
- ○ After 24 hours of ED attendance (2)

Q81 Date of discharge known?

- ○ Yes (1)
- ○ No (2)
- ○ Died before discharge (3)
- ○ Discharged/Self Discharged from the ED (4)

Display This Question:
If Date of discharge known? = Yes

Q82 Date of discharge?

_____

Q83 Documented unplanned readmission within 30 days of ED attendance?

- Yes (1)
- No (2)
- Died before discharge (3)

Display This Question:

If Documented unplanned readmission within 30 days of ED attendance? = Yes

Q84 Date of re-admission?

_____

Display This Question:

If Documented unplanned readmission within 30 days of ED attendance? = Yes

Q85 Readmission related to traumatic brain injury?

- Yes (1)
- No (2)
- Unknown (3)

Q86 Patient on TARN?

- Yes (1)
- No (2)

Display This Question:

If Patient on TARN? = Yes

Q87 Death recorded on TARN within 30 days of ED attendance?

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Death recorded on TARN within 30 days of ED attendance? = Yes

Q88 Was death within 24 hours of ED attendance?

- ○ Yes (1)
- ○ No (2)

End of Block: Default Question Block

Appendix 38: Pre and Post 2014 NICE head injury guideline sensitivity analysis of risk score performance

N=1569	**Deteriorated**	**Didn't deteriorate**	**Positive Predictive Value (PPV)** **Negative Predictive Value (NPV)**
Performance of Risk score pre 2014 NICE Guideline			
Admission (Score>0)	136	316	PPV = 30.1%
Discharge (Score=≤0)	0	23	NPV = 100%
	Sensitivity= 100% (95% CI: 96.6% to 100%)	Specificity= 6.8% (95% CI: 4.4% to 10.1%)	
Performance of Risk score post 2014 NICE Guideline			
Admission (Score>0)	287	743	PPV = 27.9%
Discharge (Score=≤0)	2	62	NPV = 96.9%
	Sensitivity= 99.3% (95% CI: 97.2% to 99.8%)	Specificity= 7.7% (95% CI: 6% to 9.8%)	

Definitions

AIS: Abbreviated Injury Severity Score

CT: Computed Tomography

ED: Emergency Department

GCS: Glasgow Coma Scale

mTBI: Mild Traumatic Brain Injury

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

NIHR: National Institute for Health Research

ROC: Receiver Operating Curve

TARN: The Trauma Audit and Research Network

TBI: Traumatic Brain Injury

Glossary

Head Injury: any trauma to the head

Mild Traumatic Brain Injury: GCD13-15 and injury to the brain or alteration of brain function due to an external force

Severe Traumatic Brain Injury: GCS<9 and traumatic brain injury identified by CT imaging

Traumatic Brain Injury: injury to the brain or alteration of brain function due to an external force