Multicenter validation of the Scandinavian Guidelines for management of minimal, mild and moderate head injury in adults: a study protocol.

Principal investigator:

Olga Calcagnile, MD, PhD
Pediatric department, Halland Hospital Halmstad

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Introduction

Traumatic brain injuries (TBI) are one of the most common reasons for patients to attend the emergency department (ED) with an estimated incidence in Europe of 260 per 100 000 for admitted TBI[1],[2],[3]. Approximately 90% of patients with TBI are defined as mild TBI (mTBI)[4]. These patients have a normal or minimally altered level of consciousness and Glasgow Coma Scale (GCS) 13 to 15 when attending the ED.
A small minority of patients with mTBI would show pathological results, such as intracranial hemorrhages or cerebral contusions on a computed tomography (CT), and even fewer need neurosurgical intervention[5]. Nevertheless, complications would be so severe, if neurosurgical intervention is delayed, that it has become common practice to subject all patients with mTBI to CT[6]. The high number of CT scans has an impact on health care resources but may also involve risk by subjecting patients through potentially harmful ionizing radiations[7].

In the past years, several independent research groups have attempted to optimize CT use in mTBI patients by forming guidelines that aim to identify patients at high risk for intracranial complications[8]. Most guidelines have been published in the past 15 years and have been validated both prospectively internally and externally; all guidelines have been shown to be safe when implemented in clinical use with few missed complications. However the number of CT scans has not been reduced dramatically, in some cases it has even increased[9].

In 2013, the new Scandinavian guidelines (SNC13) were published. They are the first guidelines that use a biomarker, S100B, as a tool for managing patients with mTBI. Although S100B has a low specificity for intracranial complications, a high sensitivity makes it suitable to be implemented into clinical practice as a tool for CT reduction.
Previous SNC guidelines have been compared to other prominent guidelines with impressive results[10]. The SNC13 have been externally validated in a retrospective multicenter center study from the USA that was underpowered for important outcomes [11]. Nevertheless, SNC13 have already been partially implemented in clinical practice in Scandinavia. However, a strict

multicenter validation has not been performed yet nor a systematic comparison to other available guidelines.

Aims

Our primary aim is to validate the performance of the SNC13 in predicting intracranial complications in adult patients presenting with traumatic head injury in Swedish hospitals. A secondary aim is to compare the performance of SNC 13 with 6 other clinical guidelines, with respect to important outcomes. Moreover, we want to explore the performances of different biomarkers in predicting intracranial complications in predefined subgroups of TBI. Finally, we want to evaluate the possibility of further improvement of the SNC13 guidelines.

Methods

Design

We will perform a prospective, multicenter, pragmatic, observational study of adults presenting with traumatic head injury at the ED.

All data necessary for analysis including predictor variables and outcome data for all the seven guidelines included in the study will be registered (table 1). Patients will be managed clinically accordingly to the judgment of the responsible physician and/or local guidelines.

Study setting and population

The study will be set in Halmstad, Malmö, Lund, Örebro and Linköping, Sweden. Hallands Hospital Halmstad (HS) is a level II trauma centre, Skåne University Hospital in Malmö and Lund (SUS)**,** Örebro University Hospital, Linköping University Hospital are level I trauma centers.

The coordinating site for the study will be HS where the statistical and the comparative biomarker analysis will be performed.

Inclusion criteria

From September 2017 we will prospectively enroll all adult patients with a GCS 9-15 that seek the ED within 24h after TBI.

Exclusion criteria

We will exclude:

- patients younger than 18 years of age;
- patients without a Swedish personal identification number due to difficulties in performing the follow up phase;

- all patients that refuse to participate.

Primary endpoint

The primary endpoint for this study will be the sensitivity, specificity, predictive values and likelihood ratios for the SNC13 for identifying traumatic intracranial complications.

Definition

Traumatic intracranial complications are defined as a composite variable of death as consequence of the TBI, need for neurosurgical intervention or marked abnormality on CT. CT abnormalities are defined as any new, acute, traumatic intracranial pathology including intracranial hematomas of any size, cerebral contusions and depressed skull fractures.

Secondary endpoints

- Measure the sensitivity, specificity, predictive values and likelihood ratios for the SNC13 for identifying patients needing neurosurgery or neurointensive care for the TBI within the first week following trauma.
- Measure the sensitivity, specificity, predictive values and likelihood ratios for the SNC13 for identifying patients with new, acute, traumatic intracranial pathology on CT including intracranial hematomas of any size, cerebral contusions and depressed skull fractures.
- Measure the sensitivity, specificity, predictive values and likelihood ratios for the SNC13 for identifying patients with clinically relevant CT findings (according to the CCHR) [12], defined as contusions larger than 5mm in diameter, subarachnoid bleeding thicker than 1mm, subdural hematoma thicker than 4mm, pneumocephaly that will need intervention, depressed skull fracture through the inner table.
- We will calculate sensitivity, specificity, predictive values and likelihood ratios of each guideline in identifying traumatic intracranial CT finding when applied to the same TBI population. We will also measure frequency of CT scans. We will investigate the performance of the SNC13 in comparison to other guidelines in reducing CT frequency without missing complications. We hypothesize that the implementation of a biomarker as S100B into clinical guidelines will achieve a further reduction in CT scans. Accuracy variables will be statistically compared with Chi-squared test.
- Measure performances of novel biomarkers such as GFAP, SBP-50 and TAU. S100B is the most studied brain biomarker and is the only one that is clinically used as a screening tool. However, S100B is not the perfect brain biomarker for TBI and new

biomarkers appear promising. In a explorative analysis we will compare S100B with GFAP, SBP-50 and TAU on the same selected mTBI population in order to determine the potential value of a panel of biomarkers for identifying high and low risk patients. We will calculate sensitivity, specificity, predictive values and likelihood ratios of each biomarker in identifying traumatic intracranial CT finding when applied to the same TBI population. ROC curves will be calculated in order to compare cut off values. We will also use the net reclassification index to see if each biomarker improves the accuracy of the classification.

- The final aspect that we would like to study is the derivation of a new improved guideline: binary logistic regressions analysis of all the variables taken into account and registered during the study will be performed. We will a priori divide the population into a derivation cohort, obtain ROC curves, and use these cutoffs after the bootstrapping process and other clinical and biochemical variables to construct a mode losing multivariable analysis.

Guidelines

A secondary goal of the study is to compare how the same mTBI population would be managed according to 7 guidelines that are clinically used in this particular patient group; we included the Canadian CT Head Rule[13] (CCHR), the New Orleans criteria[14] (NOC), the National Institute of Clinical Excellence[15] (NICE), the CT in head injury patients Prediction Rule[16] (CHIP) , the Neurotraumatology Committee of the World Federation of Neurosurgical Society[17] (NCWFNS), the National Emergency X-Radiography Utilization Study II[18] (NEXUS-II) and the SNC 2013[19].

Each guideline has specific inclusion and exclusion criteria, and outcome measures, see table 2.

For each guideline patients will be divided into different groups: those who should be dismissed without a CT, those who should do a CT and those who do not fit the inclusion criteria for the guideline. A comparison of the 7 guidelines is shown in table 3.

The CCHR includes only patients with GCS 13-15 that have suffered LOC, have amnesia for trauma or are disoriented. Patients are divided into a high risk group, where CT is mandatory because of elevated risk for neurosurgical intervention, and medium risk for CT complications, in which case CT is only recommended. Both groups are analyzed independently but reported together for the group where CT scan should be performed. The CCHR primary outcome measure is the need for neurological intervention and the secondary

outcome is clinically relevant brain injury on CT. Clinically relevant CT findings are defined as contusions larger than 5mm in diameter, subarachnoid bleeding thicker than 1mm, subdural hematoma thicker than 4mm, pneumocephaly that will need intervention, depressed skull fracture through the inner table.

The NOC includes only patients with GCS of 15, thus according to these guidelines patients with GCS 14 or less were considered to have an indication for CT[20]. The NOC outcome measure is any acute traumatic intracranial lesion on CT.

The NICE guidelines stratify patients that are eligible for CT into two groups, those who should undergo a CT within 1 hour and those within 8 hours. Both groups are analyzed independently but reported together for the group where CT scan should be performed.

The CHIP prediction rule does not have strict inclusion criteria, and recommends CT in the presence of one major or at least 2 minor risk factors. Both groups are analyzed independently but reported together for the group where CT scan should be performed. The CHIP primary outcome measure is any intracranial traumatic finding on CT, secondary outcome is all neurosurgical intervention after the initial CT.

The NCWFNS guidelines identify three levels of risk for intracranial complications. Low risk patients can be dismissed without any further investigation while patients with medium and high risk should have a CT scan and therefore are analyzed together.

NEXUS II does not stratify patients or take into account injury mechanism, it focuses mostly on symptoms at presentation at ED. The NEXUS II outcome measure is any intracranial injury on CT.

The SNC13 guidelines include all patients with head injury within 24h and a GCS 9-13. Patients with mild head injury are divided into high risk, medium risk or low risk for intracranial complications. Low risk patients (GCS 14 or GCS 15 and LOC or repeated vomiting) with normal S100B can be dismissed directly. The SNC13 primary outcome is the need for any neurosurgical intervention. The secondary outcome measures are identification of non-neurosurgical intracranial traumatic complications.

Data registration and follow-up

Details of how patients are managed, including patient characteristics, injury type, patient history, clinical examination results, current medications and CT findings will be documented in a pre-determined case-report form by the triage nurse and/or physician on call.

All patients will be asked to answer a questionnaire sent by mail 3 months after the injury. The questionnaire will be re-sent if no answer is received. If no answer is received from these

attempts, patients will be contacted via telephone. The questionnaire includes questions that would identify a significant intracranial lesion, data concerning sick-days, new contacts with medical professionals and information concerning quality of life. In cases where patients can not be reached by mail or telephone, medical records and national mortality databases will be consulted for evidence of complications and/or death. The Swedish health care system allows full visibility of data for persons with a Swedish personal identification number for medical records and mortality database over the whole country. Patients who suffer significant (enough to seek medical care) intracranial complications after discharge would therefore be identified.

Details on study period are specified on figure 1 with an algorithm for patient eligibility and data analysis.

Data will be registered in an Excel® file. Descriptive statistics will be analysed using IBM SPSS® Statistics Version 20 software.

S100B analysis

A 5ml blood sample is drawn from patient's cubital vein in the ED. Samples are analysed with the fully automated Elecsys® S100 (Roche AB) at the Clinical Chemistry Department of HS, SUS, Örebro University Hospital and Linköping University Hospital, Sweden. Cut-off level for normal levels of S100B according to the SNC guidelines is less than 0.10µg/L and a window of sampling of within 6 hours from the time of the injury.

From all patients seeking care within 24h form injury with medium and low risk TBI, according to SNC13 (including multitrauma patients), a 5ml blood sample will be drawn, centrifuged and frozen at -70 degrees Celsius. Samplings will be coded and registered for analysis of GFAP, SBP-50 and TAU.

CT examinations

CT scans are always analysed by a board certified radiologist.

Sample size

We assume that the Scandinavian guidelines will recommend discharge (i.e. neither CT nor admission) in approximately 50% of patients and a prevalence of our primary outcome of 5% (from our own observations and from data derived from a pre-selected cohort)[21]. Allowing for one missed case, a sensitivity of >99% with a lower 95% confidence interval, a sample size of 2490 patients is required to detect traumatic intracranial complications according to the SNC13. Allowing for a 10% lost to follow-up, our desired sample size is 2767 patients.

Interim analysis

After 1000 patients we will measure prevalence for the primary outcome in order to be able to reevaluate sample size.

Ethics

Ethical approval was granted from the Regional Ethical Review Board of Lund (approval number 2012/574).

Informed verbal consent will be obtained and registered by nurses responsible for triage at ED.

Patients' data and social security number will be stored and handled accordingly to Swedish Personal Data Act, (PUL 1998: 204).

Written consent will be obtained from all patients from whom the extra blood sampling for biomarker analysis will be requested. Sampling will be coded and patients will be able at any time to refuse to be part of the study.

Discussion

The main purpose of this study is to perform a prospective validation of the new SNC13 guidelines. The external validation already performed has the limitation of being applied to a preselected population; nevertheless it showed that the SNC13 have a potential impact for reducing frequency of CT scans[22]. In order to complement the previous study we designed this multicenter prospective study that will collect enough data to support the safety and efficacy of the SNC13. The study is pragmatic in nature, including all adult patients with GCS 9-13 within 24h of head injury, with very few exclusion criteria.

The second important aim was to compare the SNC13 to the other 6 guidelines. Different guidelines applied to the same population will perform with very different results, as previous studies have already shown[23],[24]. The first aspect to be discussed in this comparative work is how many patients of this TBI population could be managed according to different guidelines. Both NOC, NICE and CCRH guidelines have strict inclusion criteria that may exclude a substantial portion of the TBI patients leaving physicians with no other choice than CT. Nevertheless, more flexible guidelines with no exclusion criteria like CHIP prediction rule or the NCWFNS guidelines have been proven to only marginally reduce the number of CTs. Nevertheless, beside restricted inclusion criteria, the NICE guidelines have shown to be one of the better performing guidelines for reducing CT frequancy[23].

In the SNC13 guidelines, all patients could be managed with no exclusion criteria pre-defined, except for the time frame of 24h. According to previous studies, we would have expected a S100B negative rate for about 30% of sampled patients but, considering the new grading of patients, we expect better performances.

S100B is not the perfect biomarker for mTBI considering its low specificity. The perfect biomarker should be able to be brain specific, easily detectable, have a high sensitivity for intracranial complications and adverse outcome, with 100% negative predictive value and high clinical specificity. In recent years researchers agree on the possibility of defining a brain biomarker-panel; it therefore is fundamental to compare a well-studied biomarker as S100B with other new biomarkers. . The present study includes the most promising of these.

Strength and limitations

The main strength of this study is its design being an adequately powered multicenter study. Another important aspect is that it tests the SCN13 in the health care system for which it was intended for.

However every study has its limitation: a proper validation should be performed with a randomized study design; however this method would be ethically questionable.

The SNC13 were designed primarily for the Scandinavian health care system and its validity outside Scandinavia cannot be assumed.

Biomarker analysis will only be performed in a pre-defined subgroup of patients. This could lead to selection bias; however, the remaining patients do not have any theoretical advantage in management with biomarker results.

Variable	Data Format
Demografic/anamnestic variables	
Age	Years (continuous)
Gender	Male/female
Cause of injury	Patient report
Pedestrian/cyclist versus vehicle	Yes/no
Ejected from vehicle	Yes/no
Fall	Yes/no
Fall >1m	Yes/no
Signs of skull fracture	Yes/no
Contusion of the skull	Yes/no
Fracture above clavicles	Yes/no
Alcohol/drug intoxication	Yes/no
Ethanol levels	mmol/l (continuous)
LOC*	Yes/no
Duration LOC	Minutes (continuous)
Amnesia	Yes/no
Duration Amnesia	Minutes (continuous)
Persistent anterograd amnesia	Yes/no
Headache	Yes/no
Worsening headache	Yes/no
Vomiting episodes	Number (continuous)
Neurological deficit	Yes/no
Pretraumatic seizure	Yes/no
Posttraumatic seizure	Yes/no
GCS	Number (continuous)
GCS deterioration**	Number (continuous)
Antiplatlet medication	Yes/no
Anticoagulation therapy	Yes/no
Drug registration	Drug name
Bleeding disorder	Yes/no
Shunt-treatment	Yes/no
Dismissed***	Yes/no
S100B	µg/L (continuous)
CT	Yes/no
Admitted	Yes/no
Other causes to admission than TBI	Yes/no
Length of admission	Days (continuous)
Complications during admission	Yes/no
*** LOC= loss of conciousness** **** deterioration of GCS 2 after injury** ***** dismissed with no intervention (CT or admission)**	

Table 1. variables studied

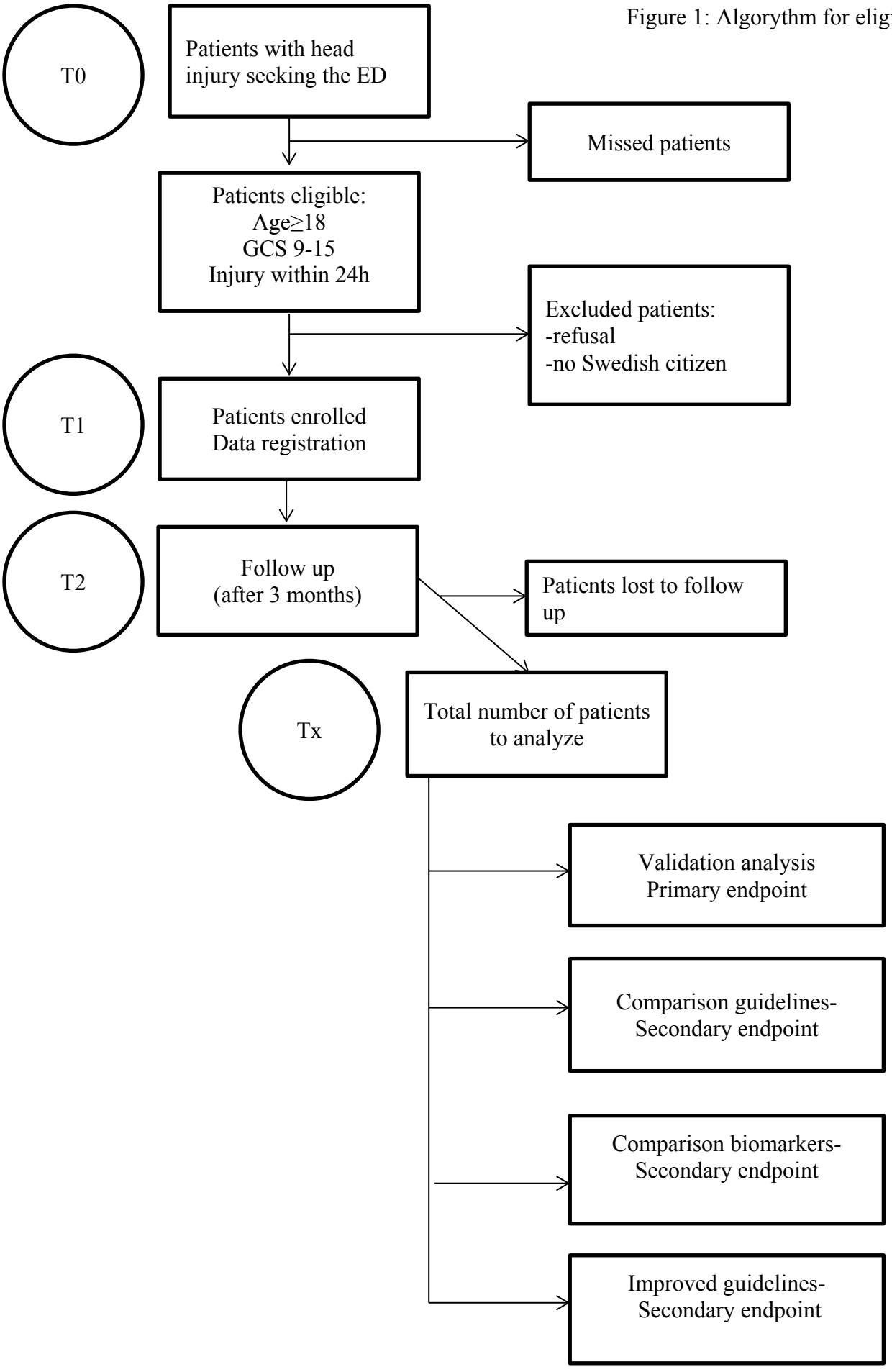
	CCHR	NOC	NICE	CHIP	NCWFNS	NEXUS II	SNC13
Inclusion criteria	Age ≥ 16 Presenting within 24h of head injury	Age ≥ 18 Presenting within 24h of head injury GCS 15	Age ≥ 18	Age ≥ 16 Presenting within 24h of head injury GCS 13-14 or GCS 15 and LOC or amnesia or pst-traumatic seizure or vomiting or severe headache or alcohol/drug intoxication or coagulopathy/ oral anticoagulants or injury above the clavicle or neurological deficit	Age ≥ 18 Presenting within 12h of head injury GCS 14-15	Age ≥ 18 GCS 15	Age ≥ 18 Presenting within 24h of head injury GCS 9-15
Exclusion criteria	-No clear history of trauma as primary event -Penetrating skull injury or depressed fracture -bleeding disorder or oral anticoagulants - neurological deficit	GCS ≤14					
Primary outcomes	Any need for neurological intervention	Acute traumatic intracranial lesion on CT		Any intracranial traumatic finding on CT		Any intracranial injury on CT	Any neurosurgical intervention
Secondary outcomes	Clinically relevant brain injury on CT			All neurosurgical intervention after initial CT			Any non-neurosurgical intracranial traumatic complications

Table 2. inclusion criteria, exclusion criteria, primary outcomes, secondary outcomes

Clinical findings	CCHR	NOC	NICE	CHIP	NCWFNS	NEXUS II	SNC 2013
Age	≥65	>60	≥65	≥60 major 40-60 minor	>60	≥65	≥65 and anti-platelet treatment
Pedestrian/cyclist versus vehicle	Minor		Minor	Major			
Ejected from vehicle	Minor		Minor	Major			
Fall >1m	Minor		Minor	Minor			
Signs of skull fracture	Any	Any	Any	Any	Any	Any	Any
Contusion of the skull						Any	
Fracture above clavicles		Any					
Alcohol/drug intoxication	Any				Any		
LOC*	Inclusion	Inclusion	Inclusion	Minor	Any		Low risk
Amnesia	Retrograde > 30 min	Antegrade	Retrograde > 30 min	≥4h major 2-<4h minor	Any	-	-
Headache		Severe			Any		
Vomiting episodes	>2	Any	>2	Major	Any	>2	>2 and GCS 14 low-risk
Neurological deficit	Excluded	Excluded	Any	Minor	Any	Any	Any
Pretraumatic seizure					Yes		
Posttraumatic seizure	Excluded	Any	Any	major	Any		Any
GCS <15	After 2h	Exclusion	After 2h	≥2 points deterioration Major 1point=minor	Always	Always	14 and no other risk-factor= low risk
Antiplatlet medication							And ≥65y
Anticoagulation therapy	Exclusion	-	Any	Major	Any	Any	Any
Bleeding disorder	Exclusion			Major			Any
Shunt-treatment					Any previous neurosurgical intervention		Yes

Table 3. Comparison of the 7 guidelines used in clinical practice for initial screening of TBI.

Figure 1: Algorythm for eligibility



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