Centre for Assessment of Medical Technology in Örebro

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A Systematic Review of the Diagnostic Performance of Serum Biomarkers in Paediatric Mild Traumatic Brain Injury

Systematisk översikt av diagnostisk tillförlitlighet hos serumbiomarkörer vid lätt skallskada hos barn (GCS 14–15)

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Region Örebro län

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The medical fact boxes in our reports are written by independent experts who were not involved in conducting the systematic review. External reviewers provide valuable feedback that improves the quality of our HTA reports. However, responsibility for the final content rests solely with Camtö. All authors and reviewers declare that they have no financial conflicts of interest related to the topic of this systematic review.

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Abbreviations

AUC	Area under curve
ciTBI	Clinically important traumatic brain injuries
CT	Computed Tomography
ED	Emergency department
FN	False negative
FP	False positive
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acid protein
HFABP	Heart fatty acid binding Protein
LR+	Likelihood ratio of a positive test
LR-	Likelihood ratio of a negative test
MHT	Minor head trauma
mTBI	Mild traumatic brain injury
NR	Not reported
NPV	Negative predictive value
NSE	Neuron specific enolase
PECARN	Paediatric Emergency Care Applied Research Network; clinical decision rule for the management of minor head trauma in children
PPV	Positive predictive value
TBI	Traumatic brain injury
TN	True negative
TP	True positive
UCH-L1	Ubiquitin carboxy-terminal hydrolase L1

Innehåll

Abstract

Background

The use of head CT in children after trauma is challenging. We aimed to summarise diagnostic accuracy studies comparing serum biomarkers with CT in patients younger than 18 years presenting with Glasgow Coma Scale (GCS) 14-15.

Methods

Medline, Embase and the Cochrane Library were searched by librarians from inception to May 30, 2025. The PRISMA reporting guidelines for systematic reviews were followed. Prospective cross-sectional studies were eligible. Risk of bias was assessed using QUADAS-2. Likelihood ratios (LRs) were calculated from extracted data, and results were narratively synthesised.

Results

Out of 316 identified studies, 117 were assessed in full text. Four studies were relevant but two had unacceptably high risk of bias and were not included in the extraction of outcome data.

One study from 2024, assessed as having a high risk of bias, included 43 children who underwent head CT at the discretion of attending physicians and biomarker testing within 6 hours. At a sensitivity fixed at 100%, the specificity was 35% for S100B, 39% for GFAP, and 37% for HFABP.

Another study from 2015, assessed as having moderate risk of bias, included 109 children who underwent head CT according to the PECARN rule and S100B within 6 hours. Sensitivity for traumatic brain injury was 76%, and specificity 63%.

Calculated LRs indicated the investigated biomarkers are not informative to clinicians.

Conclusion

Two studies with differing inclusion criteria comprising a total of 152 patients were identified. A clinical benefit of using biomarkers to guide CT use in paediatric patients presenting with a GCS 14-15 after head trauma has yet to be demonstrated.

Populärvetenskaplig sammanfattning

Plain Languange Summary in Swedish

Bakgrund

Slag mot huvudet är en vanlig orsak till att barn och ungdomar söker på akutmottagningen. I de allra flesta fall har kraften mot huvudet varit begränsad och inte orsakat några skador på hjärnan. För en liten andel kan det finnas skador inne i skallen, trots att barnet verkar ganska normalt. Frågan är om analys av blodprover kan användas för att identifiera de barn som behöver genomgå en datortomografi av hjärnan.

Syftet med detta projekt var att kartlägga studier som jämfört resultat av blodprov med vad datortomografi visar bland barn som söker efter huvudskada men som i stort sett är opåverkade.

Metod

Medicinska Biblioteket vid Örebro universitet sökte efter studier i tre databaser utan någon bakre tidsbegränsning och fram till 30 maj 2025. Relevanta studier valdes ut och granskades.

Resultat

Till att börja med påträffades 316 studier, varav 117 valdes ut och lästes i sin helhet. Fyra bedömdes till slut som relevanta men två av dem hade inte ett lämpligt upplägg och lämnades därhän.

En studie publicerad 2024 var på 43 barn i Spanien och Schweiz som gjort både datortomografi och fått blodprover analyserade. Bland de barn som inte hade någon hjärnskada på datortomografin hade dock endast en mindre andel (34 %) ett negativt blodprov, dvs andelen falskt positiva blodprov var hög. Det innebär att om man använder analys av blodprov på alla finns risk för att fler barn kommer att skickas till datortomografi trots att de inte har några skador.

En studie från 2015 var på 109 barn i Frankrike som gjort både datortomografi enligt strikta urvalskriterier och fått blodprov analyserade. Resultatet av blodproverna visar att inte alla som hade en hjärnskada på datortomografin också hade ett positivt blodprov, utan endast 76 %. Det är allvarligt eftersom om man enbart litar på blodprovet kan det medföra att man missar barn med hjärnskada. Bland de som inte hade någon skada på datortomografin hade 67 % ett negativt blodprov, dvs var tredje utan skador hade ett falskt positivt prov.

Slutsats

Två studier som tillsammans undersökt 152 barn inkluderades i vår rapport. Studierna visar att det i nuläget inte finns någon fördel med att använda blodprov för att hitta barn som behöver en datortomografi efter slag mot huvudet, utan läkarnas kliniska bedömning är bättre.

Medical fact box *(pp 7-10)*

András Büki, Professor of Neurosurgery, Örebro university

Overuse of radiation-based imaging (CT) is a major concern in modern medicine, particularly in the pediatric population. To this end, CT decision rules including detailed risk-stratification are constructed with the aim of minimizing the use of CT scanning and to increase the proportion of informed discharge and/or observation on the floor.

Some studies suggest that up to 40% of adult, and at least 10% of pediatric CT scans could be replaced by the inclusion and consistent application of biomarkers as part of the decision-making process/triage.

Unfortunately, while biomarkers are already applied in a handful of adult guidelines and contribute to reaching the above goals, we are still missing large scale diagnostic biomarker studies in the pediatric population that could establish inclusion of biomarkers into pediatric guidelines.

Specifically, most biomarker research has been performed in adults, and age-dependent physiological differences (blood–brain barrier maturity, baseline levels, extracranial sources) limit direct extrapolation. Pediatric normative ranges are poorly established, thereby the validation of research data in the pediatric, clinical TBI population is limited.

A related problem is that existing biomarkers show inconsistent sensitivity for clinically important traumatic brain injury and thus far have not demonstrated persuading superiority to validated clinical decision rules – a concern that can be solved if large scale studies provide further evidence on the clinical application of biomarkers.

Same issues like in the case of studies conducted in the adult population also affect pediatric studies such as heterogeneity of study design, analytic inconsistencies as well as confounding factors like extracranial sources of signal and hemolysis.

Some preliminary results suggest that guideline compliance can be worse in the pediatric population, favoring over-triaging as a reflection of insecurity and anxiety from the care providers' side and that may erode the potential added value of biomarkers in the triage.

As a self-fulfilling prophecy, in lack of considerable amount of evidence, no biomarker is approved by the regulatory bodies to be used in the context of pediatric TBI.

Nevertheless, upcoming large-scale studies like the recently published work by Bouvier et al. may open the field for the diagnostic application of protein biomarkers, even rationalizing the double-marker approach of GFAP-UCH-L1 that is highly disputed in adults.

Detailed clinical studies, implementational surveys and cost-efficiency studies are needed to evaluate the clinical and societal value of TBI biomarkers in the care for pediatric TBI.

Reference

Bouvier D, et al. (2024). Serum GFAP and UCH-L1 for the identification of clinically important traumatic brain injury in children in France: a diagnostic accuracy substudy. *The Lancet Child & Adolescent Health*. 2024; 9(1): 44-54

Current Guidelines in Pediatric mild traumatic brain injury – How to establish the indication of a head CT

Current clinical practice is based on four main decision rules to exclude the need for CT scanning following mild traumatic brain injury- *vide infra.*

PECARN Rule (Pediatric Emergency Care Applied Research Network)

The PECARN rule is the most extensively validated clinical decision rule for pediatric head trauma. It aims to identify children at very low risk of clinically important traumatic brain injury (ciTBI), thereby minimising unnecessary exposure to ionizing radiation from CT scans. It applies to children under 18 years of age who present in the ED within 24 hours of blunt head trauma and have a GCS score 14-15. It excludes cases of trivial injury, penetrating trauma, pre-existing neurological disorders, prior neuroimaging, or signs of intoxication. The PECARN rule stratifies patients into two age groups. For children younger than 2 years, CT imaging is recommended in the presence of GCS < 15, altered mental status, or a palpable skull fracture. Observation or CT may be considered if there is a non-frontal scalp hematoma, loss of consciousness lasting at least five seconds, a severe mechanism of injury (such as a fall greater than three feet or being struck by a motor vehicle), or abnormal behavior as reported by the parent. For children aged ≥2 years, CT imaging is indicated when there is a GCS less than 15, altered mental status, or signs of basilar skull fracture. Observation or CT may be considered in cases of repeated vomiting, loss of consciousness, severe headache, or a severe mechanism of injury (a fall greater than five feet or being struck by a motor vehicle).

NEXUS II Rule

It was originally derived in a population of adults with blunt head trauma, but transferred to pediatric populations. It applies to patients with GCS score ≥14 and includes both those with and without loss of consciousness. CT is recommended if any of the following features are present: evidence of skull fracture, scalp hematoma, neurologic deficit, abnormal level of alertness, abnormal behavior, persistent vomiting (≥2 episodes), or known coagulopathy. Children who do not exhibit any of these findings are considered low risk for clinically important intracranial injury and may not require CT imaging. In these low-risk cases, observation should be considered.

NICE Guidelines – Pediatric Head Injury

The NICE guidelines for head injury assessment in children under 16 years of age is developed and primarily applied in the UK were it has been first published in 2003 and updated in 2023. These guidelines offer a structured approach for determining when urgent CT imaging is needed in pediatric patients presenting with head trauma. They apply to all children with head injuries, including both closed and penetrating trauma, but exclude superficial facial injuries without head involvement. CT imaging should be performed within one hour of identifying high-risk features such as suspected non-accidental injury, post-traumatic seizure in a child without epilepsy, a GCS score less than 14 (or less than 15 in children under one year), a GCS less than 15 two hours post-injury, suspected open or depressed skull fracture, signs of basal skull fracture, focal neurological deficit, or a bruise, swelling, or laceration greater than 5 cm in children under one year. Additionally, CT imaging is recommended within eight hours of injury in children with moderate-risk features including witnessed loss of consciousness exceeding

five minutes, bleeding or clotting disorders, abnormal drowsiness, repeated vomiting (≥3 episodes), or a dangerous mechanism of injury such as a high-speed road traffic accident or a fall from height greater than one meter.

Scandinavian Neurotrauma Committee (SNC) (pediatric-) guidelines from 2016

The SNC-16 is a tool and a comprehensive clinical management guideline for children and adolescents (<18 years) who present with minimal, mild, or moderate blunt head trauma within 24 hours of injury. It provides risk stratification, CT indications, observation recommendations, and discharge advice, primarily applicable in clinical settings preferring observation as an alternative to immediate radiological (CT-) scanning. Despite the committee's name, coworkers from Sweden, Norway, Denmark, Iceland and Finland constructed the document.

Unlike PECARN, which is only a CT-decision rule, SNC-16 is a *full management guideline* designed for Nordic healthcare systems where observation is easily available and radiation exposure is minimized.

SNC-16 divides children into moderate, mild high-risk, mild medium-risk, and minimal (low-risk) categories based on symptoms, neurological status, mechanism, and specific pediatric risk factors (especially in children <2 years, where scalp hematomas and irritability are important).

- **Moderate** head injury (GCS 9–13): always requires CT and admission.
- **Mild high-risk:** features such as focal deficits, suspected fracture, GCS 14, or seizures → CT or at least 24 h observation.
- **Mild medium-risk:** brief LOC, amnesia, ≥2 vomiting episodes, severe headache, behavioral change, shunt, coagulopathy, or age <2 with concerning signs → ≥12 h observation (CT only if multiple risk factors or deterioration).
- **Low-risk:** normal exam, GCS 15, no concerning symptoms → short observation (~6 h) and discharge with instructions.

In practice, SNC-16 leads to fewer CT scans and more structured observation compared to PECARN, reflecting Scandinavian priorities of safety and low radiation exposure.

Rules	Inclusion Criteria	Exclusion Criteria	CT Indications
PECARN	Children <18 years, blunt head trauma, GCS 14-15	Trivial injury, penetrating trauma, neurological disorders, prior imaging	GCS <15, altered mental status, or palpable skull fracture. Depending on age, observation or CT scan should be considered if: Aged<2: non-frontal scalp hematoma, LOS ≥ 5 sec, severe mechanism of injury, or abnormal behavior reported by parents. Aged ≥ 2: repeated vomiting, LOC, severe headache, or severe mechanism of injury.
NEXUS II	Blunt head trauma, GCS ≥14	None explicitly stated	Evidence of skull fracture, scalp hematoma, neurologic deficit, abnormal alertness, abnormal behavior, repeated vomiting
NICE Guidelines	Children <16 years with head injury	Superficial facial injuries without head trauma	GCS <14, seizure, skull fracture, vomiting, LOC >5 min, bleeding disorders, dangerous mechanism
SNC-16 guidelines	Children with **minor and moderate blunt head trauma** who meet the following criteria: **Age:** Children aged **0 to 17 years** (inclusive). **Injury Type: Blunt head trauma** (non-penetrating injury). **Severity:** Initial GCS in the ED between **9 and 15**. This covers the range of: **Minimal Head Injury** GCS 15 with no risk factors **Mild Head Injury** GCS 14-15 with risk factors **Moderate Head Injury** GCS 9-13 **Time Since Injury:** Presentation to the ED within **24 hours** of the injury.	**Severe Head Trauma:** Patients presenting with a **GCS score of 8 or below.** **Penetrating Head Injury:** Injuries caused by objects penetrating the skull. **Suspected Non-Accidental Injury (Child Abuse):** Cases where the mechanism of injury is inconsistent with the findings or child abuse is suspected. **Pre-existing Neurological/Neurotrauma Condition:** Patients whose clinical picture might be significantly complicated or explained by prior conditions, such as: Pre-existing coagulopathy (though patients on anticoagulants due to an existing medical condition are sometimes addressed within the guideline as a risk factor). Pre-existing shunts or known intracranial pathology. **Inclusion in another study** that would affect their management/treatment in the ED.	Categorizes risk factors into low, intermediate, and high risk, which dictate the recommendation for CT or observation. Mandatory CT is indicated if GCS is 13 or less, or, in case of GCS 14-15 in case of posttraumatic neurological deficit, posttraumatic seizure, clinical signs of skull base fracture/depressed skull fracture. CT **OR** observation is indicated in case of GCS14, loss of consciousness over 1min, presence of a Coagulation Disorder or Anticoagulation/Antiplatelet Therapy.

References

PECARN:

Kuppermann N, Holmes JF, Dayan PS, Hoyle JD, Jr., Atabaki SM, Holubkov R, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet. 2009;374(9696):1160-70.

NEXUS II:

Oman JA, Cooper RJ, Holmes JF, Viccellio P, Nyce A, Ross SE, et al. Performance of a decision rule to predict need for computed tomography among children with blunt head trauma. Pediatrics. 2006;117(2):e238-46.

Babl FE, Oakley E, Dalziel SR, Borland ML, Phillips N, Kochar A, et al. Accuracy of NEXUS II head injury decision rule in children: a prospective PREDICT cohort study. Emerg Med J. 2019;36(1):4-11.

NICE:

Excellence. NIfHaC. Head Injury: Assessment and Early Management. National Institute for Health and Clinical Excellence: Guidance. 2023. Scandinavian Neurotrauma Committee; SNC-16: 10.1186/s12916-016-0574-x

Background

Minor head trauma among children and adolescents is a common reason for seeking medical care. The trauma is classified as mild in at least 90%. A recent Swedish study reported an incidence of 1,815 visits to emergency departments (EDs) per 100,000 children per year due to head trauma [1]. There are currently approximately 2,2 million individuals under the age of 18 in Sweden, corresponding to almost 40,000 ED visits annually after head trauma.

The incidence of clinically important traumatic brain injuries (ciTBI) is low. In a study from 25 North American EDs in 2004-06, including 42,412 children ≤18 years who presented within 24 hours of head trauma, the prevalence of ciTBI was estimated to 376 (0.9%) [2]. Neurosurgical interventions were required in 60 (0.1%) patients. The Swedish study included 5,060 paediatric patients who attended EDs due to isolated head trauma in 2016 [1]. CT scans were performed in 273 (5.4%), and intracranial injury (ICI) was detected in 33 (0.7%) patients. Four patients (0.08%) required a neurosurgical intervention.

Scandinavian Neurotrauma Committee (SNC) provide guidelines for the management of minor and moderate head trauma [3]. Patients with GCS 9-13 must be referred for CT head immediately, whereas patients with mild head trauma and GCS 14-15 are categorised into a high, medium- and low-risk group for intracranial injury. For patients with risk factors in the high- or medium-risk group, either CT or in-hospital observation of ≥ 12 or ≥ 6 hours is recommended, while patients with GCS 15 and no risk factors may be discharged. The recommendations aim to balance medical safety, i.e. ruling out significant injuries, against the risk of exposing young individuals to ionising radiation.

Specific blood-based biomarkers have been proposed to help manage the large number of patients with minor head trauma, the low frequency of significant findings, and the drawbacks associated with CT exposure; however, to date, the evidence has been found to be insufficient. The aim of this systematic review was therefore to identify and critically appraise studies investigating the diagnostic accuracy of serum biomarkers compared with intracranial injury detected by head CT in patients under 18 years of age presenting after mild head trauma and GCS 14-15.

Methods

This systematic review was preregistered on www.researchweb/fou/orebroll July, 5 2025/ ID number 285309 [4].

Research question:

What is the diagnostic accuracy of serum biomarkers in patients under 18 years of age presenting with a GCS score 14-15 after head trauma, compared with head CT?

PIROS	
Population	Patients younger than 18 years presenting with Glasgow Coma Scale 14-15 after head trauma
Index test	Serum biomarkers within 24 hours of trauma, (within 6 hours for S100B)
Reference test	Head CT within 24 hours of trauma
Outcome	Diagnostic performance of each biomarker TP, FP, TN, FN. Sensitivity, specificity, positive and negative predictive values Area under the receiver operating characteristic curve (AUC). Likelihood ratios
Study design	Prospective cross-sectional studies

Inclusion criteria

- Studies must report results for patients with GCS 14, GCS 15, or GCS 14-15
- Studies must report outcome of at least one biomarker and CT scan of the same individual
- Blood samples for S100B must have been drawn within 6 hours of head trauma
- CT scans must have been performed in reasonably close proximity to the blood draw, and no later than 24 hours after the head trauma
- No restrictions by country / healthcare providers
- Only studies published in English

Exclusion criteria

- Studies that do not report data, or separate data, for patients younger than 18 years of age
- Studies that do not report outcome of blood draws for S100B within 6 hours of head trauma, or do not report them separately
- Studies that do not report on the outcome of biomarkers in relation to CT scans, e.g. using clinical surveillance as the reference standard
- Studies that report on biomarkers in urine, saliva, or cerebrospinal fluid
- Other types of publications except primary diagnostic accuracy studies, i.e. any type of reviews, letters, case reports, conference abstracts, editorials

Literature search

Two librarians at the Medical Library, Örebro university developed the search strategies in collaboration with one of the reviewers (ML). Medline, Embase and the Cochrane Library were search from inception to May 30, 2025. The search strategy is presented in Appendix 1.

Selection

An initial screening for relevance based on titles and abstracts including all publications identified from the literature search was conducted by three independent reviewers (LB, LO, ML). Any publication selected by either reviewer proceeded to the next level. At this stage, full-text versions of all selected publications were retrieved and assessed independently for relevance by the reviewers (LB, LO, ML). Any remaining discrepancies was resolved through consensus discussions. In addition, a thorough search for cross-references in relevant systematic reviews and identified relevant primary studies was conducted and selected in the same way (ML, LB).

Risk of bias assessment

Two reviewers (ML, LO) independently assess the risk of bias for all relevant studies using the QUADAS-2 tool [5]. Any discrepancies were resolved through discussion until consensus was reached, or by consulting a third reviewer (LB). The findings were presented in a risk of bias diagram.

Statistical review

Statistical aspects of the studies, including sample size calculation, choice of statistical methods, reporting and interpretation were reviewed separately (RK).

Integrity

All authors of the finally included studies were searched for in Retraction Watch database [6]. Details in study protocols were compared with the corresponding publication. Status of the publishing journals of included studies was obtained [7].

Conflict of interest

Financial or other types of conflict of interest declared by the authors, as well as funding or any other support (scientific writing, statistics) was extracted and tabulated.

Extraction of data from included studies

Relevant studies with unacceptably high risk of bias did not proceed to data extraction, whereas relevant studies with low to high risk of bias were included. Data on basic characteristics, such as inclusion criteria, study population, setting, specific criteria for head CT, timing and biomarker(s) investigated were extracted by one reviewer (ML) and double-checked by another (LB). All relevant data on outcomes were extracted in the same manner, including reported sensitivity, specificity as well as positive and negative predictive values, in relation to the thresholds applied in the studies.

Analysis

When sufficient data were available, 2 x 2 tables were constructed to calculate TP, FP, TN, FN, positive and negative predictive values as well as likelihood ratios for positive and negative outcomes of the tests.

If deemed appropriate, and data from at least three studies would be available, a meta-analysis for each biomarker using a random-effects model was planned. If insufficient data, or pooling was found inappropriate for other reasons, such as clinical heterogeneity, a narrative synthesis was planned instead.

GRADE

In case a meta-analysis was found appropriate, a GRADE assessment would be presented.

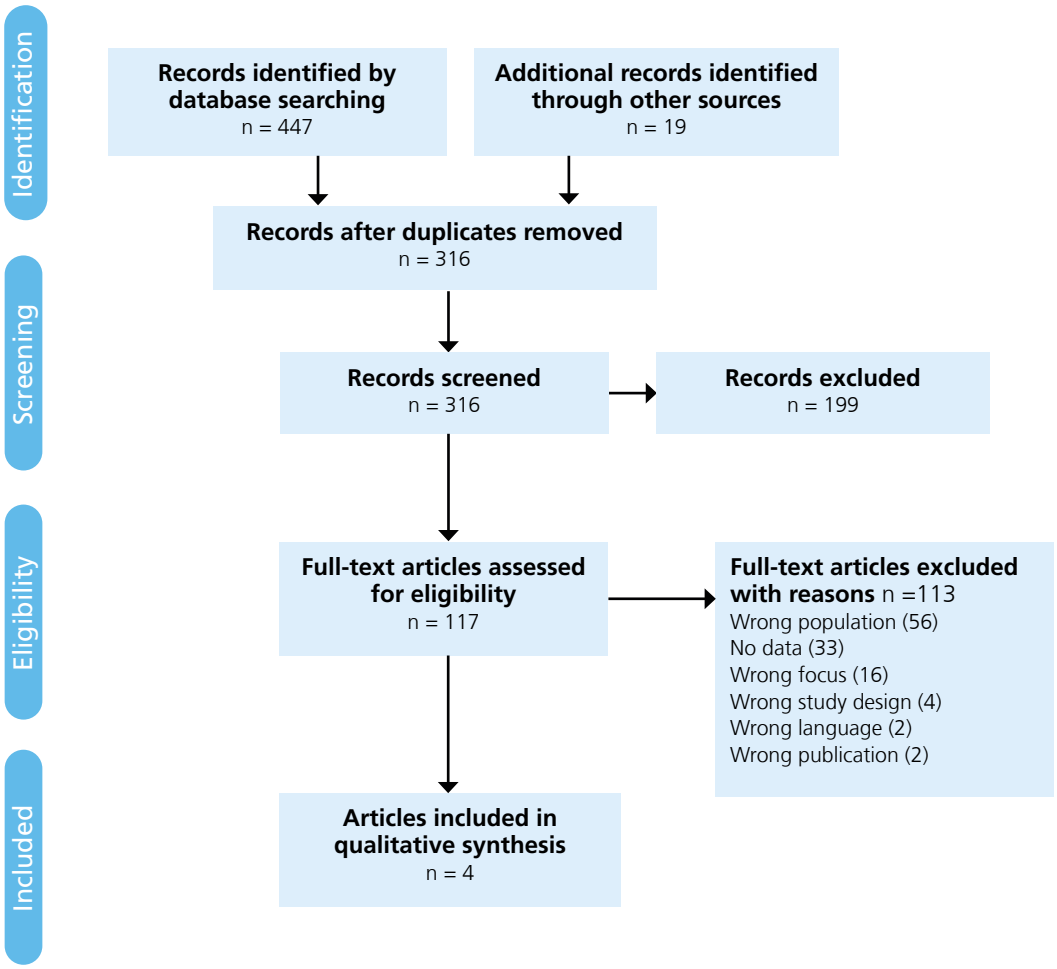
Ongoing studies

Ongoing studies were searched for in Clinicaltrials.gov [8], Clinical trials EU [9], and ISRCTN [10], and ongoing systematic reviews were searched for in PROSPERO [11].

Results

Assessment of relevant studies

The literature search yielded 447 records, with 19 additional studies identified via cross-references. After deduplication by librarians, 316 unique records remained. A total of 117 studies were read in full-text and four were found relevant (Fig. 1). Excluded studies with main reason for exclusion are in Appendix 2.



Figur 1 Study flow chart

Basic characteristics of relevant studies are presented in Table 1. The studies were published between 2015 and 2024; two were conducted in Europe, and two by the same research group in Iran. All participants were identified at pediatric EDs of university hospitals. For the study by Chiollaz et al [12], 302 patients were included but 43 had CT and blood draw within 6 hours. Seven of 43 study participants had head trauma as part of multitrauma; any such information was not reported for the other three studies. For the study by Simon-Pimmel [13], 280 patients had a head CT but 109 had a blood draw within 6 hours.

Table 1 Basic characteristics of studies identified as relevant (n= 4)

Author Year Country	N Median age Female	Inclusion period	Setting	Inclusion criteria	GCS 15	GCS 14	Symptoms at inclusion n (%)	CT criteria	Biomarker
Chiollaz 2024 Switzerland [12]	(302) **43*** 36 CT-: 6.8 7 CT+: 10.1 F 37%	Switzerland Oct 2020- Feb 2023 Spain 2019-2021	9 university hospitals 5 in Switzer- land 4 in Spain	≤16 yrs, head trauma <24 h, GCS 14-15	32	11	Headache 10 (23) Amnesia 10 (23) LOC 9 (21) Confusion 7 (16) Vomiting (>3 episodes) 5 (12) Convulsion 2 (5) Vertigo 1 (2)	No interference by the study in medical deci-sions such as to perform a CT	S100B GFAP HFABP
Mozafari 2020 Iran [14]	**CT pos:** **31** Mean 8 9 yrs F 29% **CT neg:** **31** Mean 8 yrs F 23%	2016	1 university hospital	6 mon - 18 years, incident within 6 h, GCS 14 -15	39	23	Headache 33 (53) Vertigo 10 (16) Confusion 2 (3)	Brain CT accor-ding to latest guidelines	NSE
Mozafari 2019 Iran [15]	**CT pos:** **20** 9 yrs F 20% **CT neg:** **20** 7 yrs F 40%	April- Sept 2017	1 university hospital	6 mon - 18 years, incident within 6 h, GCS 14-15	23	17	Headache 21 (52) Nausea/vomiting 23(58) Confusion 3 (8) Vertigo 3 (8) Functional neurological disorder 1 (3)	Ind. for CT scan and no history of alcohol/drug abuse, neuro-lo-gical disease, absence of seve-re traffic injury/ multiple trauma, abs-ence of melanoma	S100B
Simon- Pimmel 2015 France [13]	(280) **109*** 6 yrs F 36%	Sept 2012- April 2014	1 university hospital	< 16 yrs, incident within 6 h, GCS 14-15	56	53	Headache 16 (15) LOC 15 (14) Nonfrontal hematoma 13 (12) Vomiting 13 (12)	According to PECARN clinical decision rule	S100B

GFAP: Glial fibrillary acid protein; HFABP: Heart fatty acid binding Protein; NSE: Neuron specific enolase; LOC: Loss of consciousness; S100B: S100 calcium-binding protein B.
*number of patients that had both head CT and biomarker within time limits according to our PICO.

The study by Chiollaz [12] is based on two cohorts of children exposed to mTBI in Spain and Switzerland. The cohorts were preregistered in two separate study protocols on ClinicalTrials; the Spanish cohort focused on HFABP [16], and the Swiss cohort on biomarkers without any further specification [17]. No preregistration was found for the other three studies.

Risk of bias assessment

The study by Chiollaz [12] was running at nine different EDs during two or three years. In all, 302 patients with GCS 14-15 were recruited, and 222 of them had blood sampling for S100B within 6 hours and of these, 43 patients had a CT scan. The study did not interfere in the decision to perform a CT. This means most included patients did not receive the reference standard because this decision was at the discretion of the attending physician. It is not stated whether the index test was conducted without knowledge of the reference test, but all CT scans were reviewed by a radiologist blinded for all other information (Figure 2).

The two studies by Mozafari et al published in 2020 [14] and 2019 [15], respectively, claim the studies were conducted according to the STARD guidelines. However, in both studies an equal number of patients with and without intracranial injuries on CT were included (20/20 and 31/31). There is no explanation on how these participants were selected. Based on this unclear selection, we find both studies are associated with an unacceptably high risk of bias. According to the 2019 Mozafari study, the CT scans were independently interpreted by a consultant neurologist. In the study from 2020, it is stated there were two independent readings of the CT scan by an emergency specialist and a neuroradiologist. Neither of the studies described the brain injuries detected on CT scans.

The fourth study by Simon-Pimmel [13] is based on the PECARN (Pediatric Emergency Care Applied Research Network) clinical decision rule to classify children according to their risk of clinically important TBI (ciTBI) [18]. These include the following: death from TBI, neurosurgical intervention for TBI, intubation for more than 24 h for TBI, or hospital admission of 2 nights or more for TBI on cranial CT. However, in spite of the PECARN rule, the rate of CT use continued to be high, and the aim of the study was to investigate whether adding S100 B to the clinical assessment could help reduce the use of CT.

Only children who underwent a CT scan according to the PECARN rule were eligible for the study by Simon-Pimmel, ie this is a selected group. Out of 2,967 children with GCS ≥14 who visited the ED during the study period, 280 patients who underwent cranial CT were identified. Among these 280, 125 were missed, because of insufficient sampling, or presenting more than 6 hours after trauma. For another 44 children, the blood samples were collected more than 6 hours after the trauma and two children had pre-existing neurological disorders. Finally, 109 out of the 280 (39%) who underwent CT scan were included. The impact of this selection is unclear. It is also worth noting that we were not able to identify any preregistration or published protocol for this study.

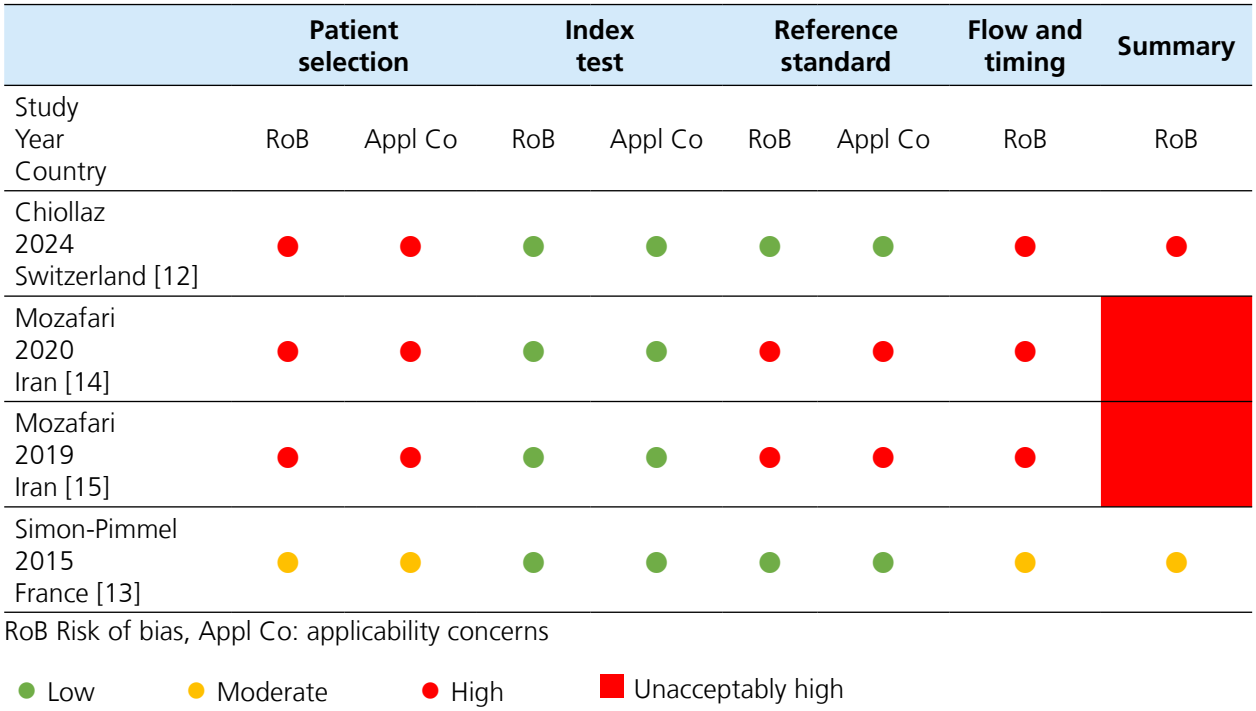


Figure 2 Risk of bias assessment of relevant studies

Statistical review

No sample size calculation is reported in the study by Chiollaz, and the adjustment for multiple testing is unclear. This is important to avoid false positive results. A 95% confidence interval was used to calculate the sample size in the study by Simon-Pimmel, but the source of the values used for this interval is unclear. It is not clear whether the researchers adjusted for multiple testing. An error was found in their flowchart reporting 16 TBI, whereas the text says 17, and 17 was confirmed by email from the first author to be the correct number in October, 2025.

Table 2 Review of statistical aspects of relevant studies (except for those of unacceptably high risk of bias)

Author Year	Sample size calculation	Analysis	Reporting	Interpretation of statistical outcomes
Chiollaz 2024 [12]	Missing	OK	Multiplicity correction is not mentioned	OK
Simon-Pimmel 2015 [13]	No reference for choice of effect size and width of CI	OK	Multiplicity correction is not mentioned Figure 2 shows 16 TBI, but the author confirmed by email 17 is the correct number	OK

Integrity

All authors of the relevant studies were checked in Retraction Watch Database. One of 22 authors in the study by Chiollaz et al had two studies retracted in 2024. No author of the other studies was identified in this database.

Conflict of interest

No financial conflicts of interest were reported in the studies (Table 3).

Table 3 Financial conflict of interest of interest and funding

Author, Year Country	Number of authors	Financial COI in relation to sponsor N (%)	Funding
Chiollaz, 2024 Switzerland [12]	22	The authors declare no COI.	A private grant from Hôpitaux Universitaires de Genève for its first year of recruitment.
Mozafari, 2020 Iran [14]	4	The author declare they have no COI.	Support for thesis at Ahvaz Jundishapur University
Mozafari, 2019 Iran [15]	6	NR	Support for thesis from Ahvaz Jundishapur University
Simon-Pimmel, 2015, France [13]	8	The authors report no COI.	NR – the authors did not describe any source of funding, external or internal

Journals

None of the studies were published in journals of the highest quality according to "Norwegian list". Two of them were not included in the list.

Table 4 Publishing journals of the relevant studies

Author, Year Country	Journal	Type of journal	DOAJ*	Predatory reports Cabells	Norwegian list**
Chiollaz, 2024 Switzerland [12]	Neurotrauma Reports	Open Access	Yes	No	1
Mozafari, 2020 Iran [14]	Open Access Emergency Medicine	Open Access	Yes	No	Not listed
Mozafari, 2019 Iran [15]	New Zealand Journal of Medical Laboratory Science	Open Access	No	No	Not listed
Simon-Pimmel, 2015 France [13]	Shock	Hybrid	Irrelevant	No	1

* Directory of Open Access Journals, only relevant for these journals
** Norwegian list: 0 not approved; 1 the majority of legitimate, peer-reviewed scientific journals; 2 leading scientific publication channels.

Summary

Four studies met our PICO and inclusion criteria. Two of them were found to have an unacceptably high risk of bias and lacked a description of critical aspects of their methodology. Based on this assessment, we found these studies would not contribute to clarifying the evidence base for our research question.

For the two remaining studies by Chiollaz [12] and Simon-Pimmel [13], bias of selection was also more or less problematic. However, given the low prevalence of intracranial injury among children presenting with GCS 14-15 to EDs after head trauma, it is hardly possible to design a study where all children in this group are referred for CT. In the study by Simon-Pimmel, selection for CT was deservingly based on a clear clinical rule, in all, we found that both studies contribute to the current state of knowledge. This means that the evidence presented in the next section is based on in total 152 study participants: 88 with GCS 15 and 64 with GCS 14 (Table 1). Moreover, due to heterogeneity in CT utilisation criteria as outlined above, the findings will only be presented descriptively and without any direct comparison.

Results reported in the included studies

Biomarker S100B

Both studies, by Chiollaz [12] and by Simon-Pimmel [13], reported findings related to S100B (Table 2). Chiollaz et al had no prespecified cutoff values whereas the study by Simon-Pimmel used age-specific thresholds for pre-specified cut-off values for 0-3 months, 4-9 months, 10-24 months and >24 months.

The study by Chiollaz reported on 43 patients; seven had traumatic brain injury and 36 had a normal CT scan outcome (Table 5). The concentrations of S100B ng/L in patients with injuries was 191(± 198) versus 92.4 (± 80.5) in patients with no injuries. When the cutoff was set at 100% sensitivity (S100B 43 ng/L), the specificity was 34%. Area under the curve at the same cutoff was 67% (95% CI 43-90). Likelihood ratios for positive and negative tests are calculated and presented in Appendix 3.

The study by Simon-Pimmel reported on 109 patients who underwent CT and had serum samples collected within 6 hours. According to the PECARN criteria, these patients were classified into high-, intermediate, and low-risk groups for ciTBI, with 60, 47, and 2 patients respectively. Of these, 17 had TBI (Table 5). We extracted data for all 109 included patients of all three PECARN risk groups in a 2 x 2 table (Appendix 3, Table 2a), and the findings translate into a sensitivity for TBI of 76%, and a specificity of 63% (Table 5).

In patients with high-risk of ciTBI; 12 of 30 patients with positive S100B had TBI, and 3 of 30 with negative S100B had TBI. This translates to a sensitivity for TBI of 12/15 (0.8) for S100B, and a specificity of 0.6 (Appendix 3, Table 2b). In patients with intermediate risk of ciTBI; one of 17 patients with positive S100B had TBI, and one of 30 patients with negative S100B had TBI. This translates to a sensitivity of 1 out of 2 for S100B, and a specificity of 0.64 (Appendix 3, Table 2c). For the 2 patients with low risk of ciTBI; both had a negative S100B, and none of them had TBI on the CT scan.

Likelihood ratios for positive and negative tests for all PECARN groups are presented in Appendix 3. The highest LR (+) was 2.05, and the lowest LR (-) 0.33. The number of CT used and the proportion of TBI missed at different scenarios on the use of S100B in the PECARN groups are outlined in Appendix 3, Table 3.

Table 5 Distribution of intracranial injuries and accuracy of S100B as reported in included studies

Author Year Country	Outcome of cranial CT		Outcome of S100B				
	Traumatic brain injury	Normal	Sensitivity %	Specificity %	PPV%	NPV%	AUC %
Chiollaz 2024 Switzerland [12]	**Distribution:** Intracranial hemorrhage or contusion 5 (71%) Pneumocephalus 5 (71%) Diastasis of the skull 2 (29%) Midline shift of intracranial contents 1 (14%) Depressed skull fracture 1 (14%)		**100% sensitivity at threshold 43 ng/L**	34	NR	NR	67
Subtotal	7	36			-		
Simon-Pimmel 2015 France [13]	**Distribution:** Intracranial contusion 1 (6%) Intracranial hemorrhage 10 (60%) Diastasis of the skull 2 (11%) Pneumocephalus 3 (17%) Depressed skull fracture 1 (6%) Total: 17 patients		76 (13/17)*	63 (58/92)*	NR	NR	NR
Subtotal	17	92			-		
Total	**24**	**128**			-		

NR: not reported, AUC: area under the curve
*numbers extracted from Figure 2 in the study by Simon-Pimmel et al.
Corresponding 2x2 table is in Appendix 3, Table 2a.

Biomarkers GFAP and HFABP

The biomarkers GFAP and HFABP were only investigated in the study by Chiollaz et al [12].

Mean value of GFAP (ng/L) for patients with a CT showing TBI was 1820 (± 2,460), and for patients with a negative CT it was 737 (± 967) (p= 0.084). Mean value of HFABP (ng/L) for patients with a positive CT showing TBI was 5470 (± 3,960), and for patients with a negative CT it was 4,710 (5,280) (p= 0.34). When sensitivity was set at 100%, the corresponding specificity was 39% for GFAP, and 37% for HFABP (Table 6). Specificity for combinations of the biomarkers GFAP, HFABP and S100B when sensitivity was set at 100% was estimated to 57-68%.

Table 6 Specificity when threshold was set for 100% sensitivity for GFAP and HFABP and combinations

Author Year Country	Biomarker	Threshold for 100% sensitivity (ng/L)	Specificity %	AUC %
Chiollaz, 2024 Switzerland [12]	**Single biomarker**			
	GFAP	204	39	71
	HFABP	2457	37	62
	Combination of biomarkers			
	GFAP / HFABP	214 / 2457	68	NR
	GFAP / S100B	214 / 44	66	NR
	HFABP / S100B	2457 / 44	57	NR

AUC: area under the curve

Summary of Findings

S100B

Outcome	Number of studies Participants (n)	RoB	Directness	Consistency	Precision	Summary
Diagnostic performance of biomarker	2 (152)	High/moderate	Yes	Inconsistent findings	Small numbers	Insufficient data; any conclusion not possible.
Area under ROC curve	1 (43)	High	Yes	Only one study	Small numbers	Insufficient data; any conclusion not possible.
Likelihood ratios	2 (152)	High/moderate	Yes	LR+ and LR- both insufficient for clinical purposes		Two small studies show the discriminatory abilities of S100B is insufficient for clinical purposes.

Ongoing studies

Primary studies

ClinicalTrail.gov was searched 2025-10-16 and the BRAINI2 study (Blood Biomarkers to Improve Management of Children With Traumatic Brain Injury) was found, registered in June 2022 (Study Details | NCT05413499 | Blood Biomarkers to Improve Management of Children With Traumatic Brain Injury | ClinicalTrials.gov). A protocol was published in May 2024 [19]. The aim is to conduct a multicentre study in France, Spain and Switzerland and include 2,880 patients younger than 18 years. One purpose is to assess the performance of an automated test combining GFAP and UCH-L1 developed by bioMérieux (the VIDAS® TBI) in 630 children with mild TBI (GCS 13-15) compared to head CT. The status of the study is now presented as unknown on the website, and we had no reply to our email request.

Clinical Trials in the European Union - EMA and ISRCTN Registry were searched 2025-12-10 but no relevant protocol was identified on these websites.

Systematic reviews

A systematic review was registered on PROSPERO (CRD42024588121) in 2024 by a group of radiologists in Australia. It proposes to cover S100B, GFAP, UCH-L1, NSE, and IL-6 in patients aged 0 – 18 years with mTBI, and determine sensitivity, specificity, positive and negative predictive values, and area under the curve (AUC) for these biomarkers compared to cranial CT as the reference standard. The systematic review was completed in November 2025 according to the website, but has not yet been published.

Another systematic review "Systematic review of blood-based biomarkers to exclude the presence of intracranial injuries on suspected mild traumatic brain injuries (mTBI)" was registered on PROSPERO (CRD420251051158) in May 2025. The aim is to assess the accuracy of blood-based biomarkers to predict intracranial injuries following a suspected mild TBI.

Discussion

Two studies evaluating biomarkers vs CT findings in patients younger than 18 years of age presenting with GCS 14-15 after head trauma were included. However, the included study populations were selected because CT was performed either at the discretion of the attending physician or according to the PECARN rules. Consequently, the studies are not readily comparable, and any summarising finding of the diagnostic accuracy of biomarkers vs CT findings is not possible. The conclusion of this systematic review is therefore limited to a descriptive evaluation of the performance of the investigated biomarkers, which was found to be insufficient for clinical use.

S100B was the only biomarker investigated in both studies. One of the studies, by Chiollaz [12], reported a specificity of 34% of S100B when the sensitivity was set at 100%. The other study by Simon-Pimmel [13] proposed an integration of S100B into the clinical PECARN decision rule to and they concluded that they had showed "that combining a validated clinical decision rule (PECARN) with a validated biomarker for the management of head trauma allows a significant decrease in CT scans". However, we find their findings rather demonstrate the risk of adding S100B to the clinical decision rule. Based on the preset threshold, the sensitivity of S100B for all 109 patients included was only 76%, and even in the high-risk group according to the PECARN rules, 3/30 (10%) patients with a negative S100B had a TBI.

We calculated positive and negative likelihood ratios based on the findings in these two studies. Likelihood ratios show the ability of any test to distinguish between patients with and without the disorder regardless of the prevalence. In none of our calculations this ability was present for S100B.

One of the excluded studies published in 2025 is of interest [20]. This is an ancillary diagnostic substudy to the PROS100B cluster-randomised trial, including 2,078 participants at 11 centres in France published in 2024 that found no significant differences in the use of cranial CT between the groups allocated to S100B monitoring or not [21]. The aim of the substudy was to investigate the diagnostic value of GFAP and UCH-L1 in children under 16 years of age who presented with GCS 15. But nota bene, only patients whose S100B levels exceeded the threshold for head CT were included, i.e. all patients in the substudy therefore represent a selected group (i.e. 531 mTBI cases). This was not compatible with our PICO.

In the study, 68/531 patients were subjected to cranial CT. However, the outcome of the CT scans are not reported in relation to the outcome of the biomarkers, i.e. an exclusion criterion for our systematic review. Instead, the outcomes of the biomarkers are reported in relation to ciTBI. Based on in total ten patients with ciTBI, the combination of GFAP and UCH-L1 had a sensitivity of 100% and a specificity of 67%. This could be the beginning of an important improvement but the findings are still quite preliminary given the very low number of patients included in the calculations.

We only included studies on patients with GCS score of 14 and 15 at presentation. This restriction was determined by the SNC guidelines as patients with GCS 9-13 are recommend-ded to be referred for

CT scan directly, and there is no need for biomarkers in this group. This restriction also meant that the number of potentially eligible studies decreased. If we had included studies also based on patients with GCS 13, another eight studies would have been available. We may have lost some information by not including these studies, but on the other hand it would have been very difficult to interpret the findings and disentangle the outcome for the group of GCS 14-15.

For the very same reasons we had to exclude studies by Papa et al [22], that did not present data for participants under the age of 18 and GCS 14-15 specifically on GFAP and UCH-L1 separately. This was disappointing as this combination was recently approved by FDA.

We chose outcome of CT scans as our gold standard, fully aware of that not all findings on the scans are of clinical relevance. However, CT readings are more standardised and less influenced by other factors, such as local routines, traditions, and complications related to multi-trauma, which could have been a problem if we had selected chosen a more clinically driven outcome.

There is currently strong hope among advocators for biomarkers that these may pinpoint children at high risk for intracerebral injuries [23], even if diagnostic cutoffs have not yet been fully investigated [24]. However, the impact of the low prevalence of traumatic brain injury in the paediatric population, and even lower for TBI that requires neurosurgical interventions, means anything but at very high specificity will affect the positive predictive value of any biomarker. For instance, at a prevalence of 1%, e.g. as for intracranial injury, increasing the specificity of a test from 33% to 66% will only increase the PPV from 1.5% to 3%. It means that the overwhelming majority of children with a positive biomarker will have a negative CT scan. The impact of such a low prevalence, and the relation with specificity and PPV, is outlined in Appendix 4.

In conclusion, there is currently no convincing evidence favouring the use of biomarkers to guide the use of CT among patients under the age of 18 years after mild head trauma. Adding biomarkers to the clinical pathway may even risk increasing the numbers of patient that will be exposed to radiation.

We understand it would be impossible, or rather it would be medically incorrect to aim for zero head CT in patients under the age of 18 years who present with GCS 14-15 after head trauma. The actual use of head CT in this group must therefore be meticulously investigated in order to understand the magnitude of the clinical problem of too many head CT that biomarkers are intended to solve (see Statistics from Region Örebro län).

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Ethical reflections

Head trauma is a very common reason why individuals might need medical evaluation. The skull is a tight connection of bones in order to protect the brain. Injuries in the head region easily initiate worries for damage to the brain.

The diagnostic process must balance on the one hand the risk for unnecessary CT-scans, with resulting exposure to radiation, and also a misuse of resources - and on the other, the risk of missing intracerebral damage which might necessitate surgical or other intervention. With the intent to reduce CT-use, biomarkers have been introduced. This systematic review examines the evidence for the assumption that they can replace, or at least complement, CT scans in case of head traumas in children and adolescents with GCS 14-15.

Only two studies were included in the final selection. A further two which reached the final selection were excluded due to unacceptably high risk of bias, but even the two finally included studies have a high risk. This is, of course, unsatisfactory and makes the ethical evaluation more difficult. The lack of evidence delays the introduction of biomarkers and raises questions about their overall usefulness for this purpose.

Can overseeing an intracerebral damage after a head injury mean grave risks for the patient? In the medical background, it is noted that only a very small part of those with detectable intracerebral damage need neurosurgical intervention. It remains unclear to which extent those with detectable damage but no need for operation profit from the CT-detection. Would they, undiagnosed, have healed their injuries, and at the same time avoided the risk of being traumatized by the very knowledge that ”something is wrong inside the skull”?

The ethical basis for the use of these biomarkers as a replacement for, or complement to, CT-scans relies on their sensitivity, which must be very high, and their specificity, which must also be high, otherwise unacceptably many false negatives and positives will result. Missed diagnoses of intracerebral trauma are in young persons potentially dangerous, and false positives will result in unnecessary investigations, increasing the total load of ionizing radiation.

The ethical balancing which is illuminated by this report is of a kind that is often encountered in clinical ethics. Risks and benefits are weighed against each other, on often insufficient evidence basis. The most reasonable, way to handle this is to wait for further evidence, until it can be considered sufficiently solid. Currently, ethical considerations argue against clinical adoption of biomarker-guided use of head CT in the investigated population.

Statistics from Region Örebro County

In this section, we present data regarding visits to the emergency department (ED) and the number of head CT provided by Produktionsenheten, and the Department of Radiology in Region Örebro län. All data were anonymized and provided on a group level.

Emergency department Örebro University Hospital

The number of children attending the ED (paediatric or surgical) in Örebro during 2010-2013 and who were registered with S09.9 (unspecified injury of head) as the presenting complaint (not final diagnosis) is presented in Table 7. The average number of patients per year was 1,160 in 2010-2016 compared to 1,113 per year during 2017-2023. A clear drop was noted during the pandemic 2020-21.

Table 7 Number of patients younger than 18 years attending the emergency department in Örebro University Hospital between 2010 and 2023 due to unspecified head trauma (S09.9)

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Girls														
0-6 months	35	57	52	55	62	60	45	34	45	32	31	24	19	22
6-12 months	57	64	46	71	59	62	75	49	68	82	57	59	74	51
1-3 yrs	120	129	139	122	163	118	127	122	143	142	92	119	128	118
3-6 yrs	65	69	84	95	98	91	87	88	90	87	71	87	70	81
6-12 yrs	81	89	91	81	74	85	90	100	107	103	99	110	104	91
12- <18 yrs	77	74	88	92	82	92	85	76	73	105	68	95	81	102
Subtotal	**435**	**482**	**500**	**516**	**538**	**508**	**509**	**469**	**526**	**551**	**418**	**494**	**476**	**465**
Boys														
0-6 months	51	61	48	55	48	45	41	33	43	35	24	31	20	27
6-12 months	63	59	60	76	78	66	99	73	69	63	43	51	48	55
1-3 years	151	173	163	185	149	154	153	150	173	172	151	133	182	173
3-6 years	101	104	108	138	122	121	133	123	126	131	123	104	114	150
6-12 years	116	156	157	156	138	151	178	145	144	178	153	148	149	181
12- <18 years	95	101	98	122	111	121	128	111	81	100	89	82	106	109
Subtotal	**577**	**654**	**634**	**732**	**646**	**658**	**732**	**635**	**636**	**679**	**583**	**549**	**619**	**695**
Total	**1012**	**1136**	**1134**	**1248**	**1184**	**1166**	**1241**	**1104**	**1162**	**1230**	**1001**	**1043**	**1095**	**1160**

Mean number of patients attending the ED in Örebro for unspecified head trauma during 2010-2023 by age and sex is summarised in Figure 3. From the age of one this is more common among boys.

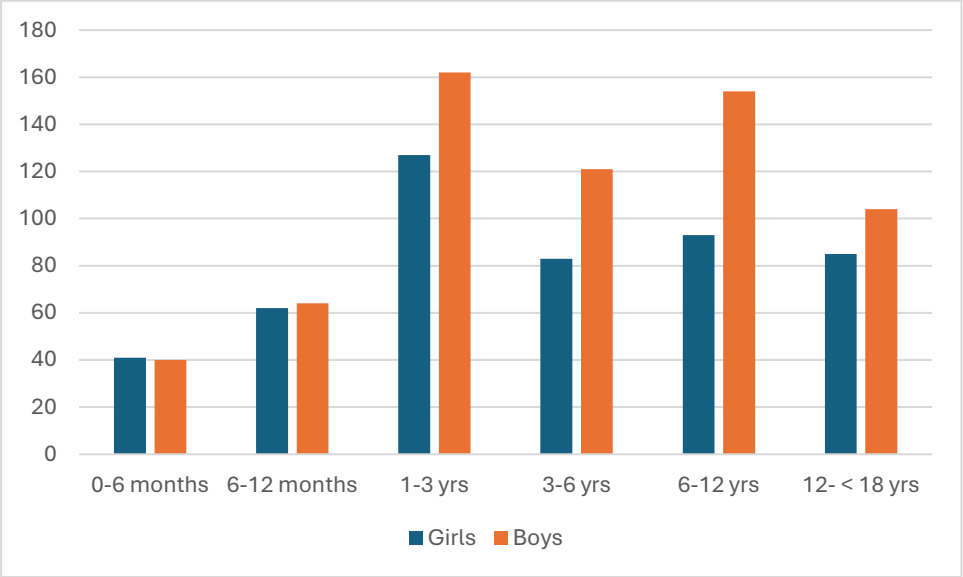

Figure 3 Average number of patients attending the ED in Örebro per year registered as S09.9 during 2010-2023 by age and sex

Data for all Region Örebro County

The number of inhabitants in Region Örebro County under the age of 18 years increased by 10% between 2010 and 2024 (Table 8). The numbers were quite stable between 2017 and 2023.

Table 8 Number of inhabitants 0-18 years in Region Örebro County in 2010-2024. *Data source: Statistics, Sweden*

Year	N
2010	60,456
2015	62,727
2020	67,429
2024	66,335

The number of patients younger than 18 years attending any of the three EDs in Region Örebro County (Karlskoga, Lindesberg, Örebro) between 2017 and 2023 has also been quite stable, except for the drop during the pandemic (Table 9).

Table 9 Number of patients < 18 years registered as S09.9 at all three EDs in Region Örebro County 2017-2023

	2017	2018	2019	2020	2021	2022	2023
Karlskoga	264	225	241	202	242	268	253
Lindesberg	138	132	141	131	125	167	168
Örebro	1104	1162	1230	1001	1043	1095	1160
Total	1506	1519	1612	1334	1410	1506	1519

Head CT *for all indications* in Region Örebro County in patients younger than 18 years decreased between 2017 and 2024 (Figure 4). In 2010, there were 396 head CT in this group and in 2024 there were 261. In 2024, rate of head CT in individuals under the age of 18 years was ~260/66,000, or 0.4% per year.

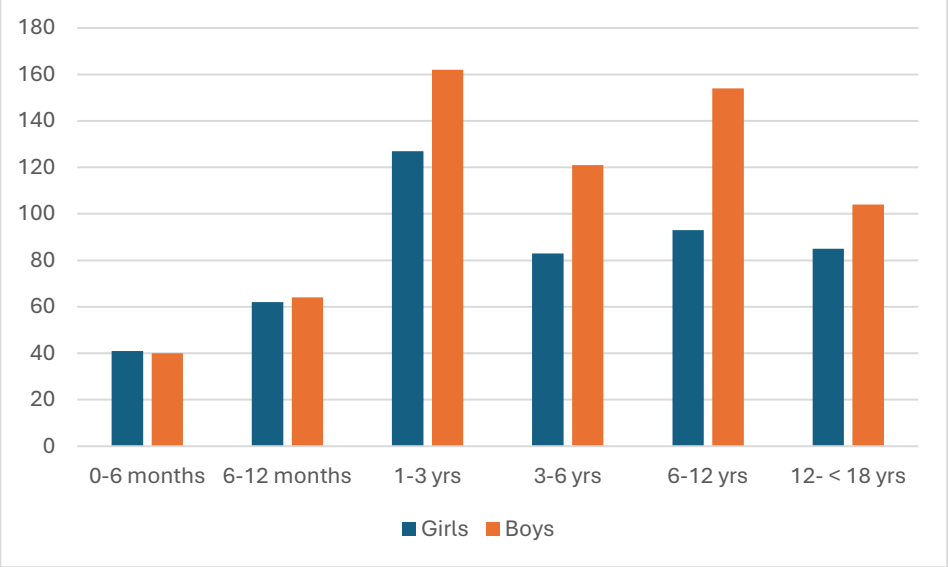

Figure 4 Annual number of head CT per year for patients <18 years in Region Örebro County

In summary, the number of inhabitants younger than 18 years of age in Region Örebro County increased by some 10% between 2010 and 2024, while the number seeking medical care for unspecified head injury seems not to have increased at the same rate. A downward trend for head CT *all indications* was observed for patients under the age of 18 years.

The estimated rate of head CT scan *all indications* for children and adolescents was 4/1,000 in 2024 in Region Örebro County. Experts must evaluate to what extent this is of great concern. However, a strong societal risk awareness regarding children's safety, and a healthcare system with low medico-legal pressure allowing clinicians to base decisions on professional judgement rather than litigation concerns, may already have limited the scope for additional reductions in the rate of head CT in this age group by biomarkers.

Appendices 1-5

Appendix 1 Literature search strategies

Database: Database(s): Ovid MEDLINE(R) ALL 1946 to May 29, 2025

Host: Ovid

Date searched: 2025-05-30

Limits applied: publications in English or Swedish language

Concept	#	Search	Results
Traumatic brain injury	1	exp Head Injuries, Closed/ or exp Brain Injuries/ or Brain Injuries, Traumatic/ or Brain Concussion/ or Brain Contusion/ or Craniocerebral Trauma/	111795
	2	("brain injur*" or "head injur*" or "head trauma*" or "cranial trauma*" or "craniocerebral trauma*" or "cerebr* injur*" or "brain trauma*" or "traumat* brain injur*" or TBI or "brain lesion*" or "cerebral lesion*" or "cerebellum injur*" or "brain concussion*" or "brain contusion*" or "cerebrum lesion*" or "intracranial injur*" or "mild traumatic brain injur*" or "minor traumatic brain injur*" or "mild head injur*" or "minor head injur*" or "minor head trauma" or mTBI or "cerebral concussion" or commotio).ab,kf,ti.	158615
	3	1 or 2	194273
Biomarkers	4	"Glial Fibrillary Acidic Protein"/ or "Ubiquitin Thiolesterase"/ or "S100 Calcium Binding Protein beta Subunit"/ or "Neurofilament Proteins"/ or "tau Proteins"/ or exp MicroRNAs/ or Myelin Basic Protein/ or exp "Fatty Acid-Binding Proteins"/	208374
	5	UCHL1 protein, human.mp.	773
	6	(S100B or "S100 B" or "S 100B" or "S100beta" or "S100 beta" or "S 100beta" or "S100 calcium-binding protein B" or "S100 calcium-binding protein beta" or "S100 subunit beta" or "protein S100beta" or "S 100 B protein" or "S 100 calcium binding protein beta subunit" or "S100 calcium binding protein B" or "S100 calcium binding protein beta subunit" or "S100 protein beta subunit" or "S100beta protein" or GFAP or GFA or "gfa protein" or "glia fibril acidic protein" or "glia fibril acid protein" or "glia fibrillary acidic protein" or "glia fibrillary acid protein" or "glial acidic fibrillary protein" or "glial fibrillary acid protein" or "glial fibrillary acidic protein" or "glia filament protein" or "glial filament protein" or " glial fibrillary protein" or "glial filament protein" or "protein gfa" or UCHL-1 or UCHL1 or UCH-L1 or "ubiquitin c-terminal hydrolase" or "ubiquitin c-terminal esterase" or "ubiquitin thiolesterase" or "ubiquitin c terminal thiolester hydrolase" or "ubiquitin carboxy terminal esterase" or "ubiquitin carboxy terminal hydrolase" or "ubiquitin carboxyl terminal hydrolase" or "ubiquitin carboxyl terminal esterase" or "ubiquitin carboxyterminal hydrolase" or NFL or NF-L or "NF L" or NEFL or NFM or NF-M or NEFM or "neurofilament protein" or "neurofilament light" or "neurofilament medium" or tau or miRNA* or MicroRNA* or "Micro RNA*" or NSE or "neuron-specific enolase" or mbp or "myelin basic protein" or MBP or H-FABP or "heart fatty acid binding protein" or "heart type acid binding protein" or "heart specific fatty acid binding protein" or "muscle fatty acid binding protein").ab,kf,ti.	307257
	7	4 or 5 or 6	356917
Children	8	exp adolescent/ or exp child/ or exp infant/ or (adolescen* or babies or baby or boy or boys or boyhood or girlhood or child* or girl? or infan* or juvenil* or kid or kids or minor* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.	5643621
Computed tomography	9	exp Tomography, X-Ray Computed/	523574
	10	(tomograph* or "ct x ray" or "ct x rays" or "cine ct" or "ct scan*" or "ctt scan*" or "cat scan*" or "catting" or "x ray ct" or "x rays ct" or "emi scan*" or "computerised axial tomogram*" or "computerized axial tomogram*" or "computerized tomogram*" or "zonograph*" or CT or CCT or "cranial computed tomograph*").ab,kf,ti.	892070
	11	9 or 10	1077565
Combined sets	12	3 and 7 and 8 and 11	213
	13	limit 12 to (english or swedish)	199

Field Codes: /:Mesh-term; exp: Exploded Mesh-term; ab: Abstract; kf: Keyword heading word; ti: Title.

Database: Embase

Host: Embase.com

Date searched: 2025-05-28

Limits applied: publications in English or Swedish language

Concept	#	Search	Results
Traumatic brain injury	1	'brain injury'/exp OR 'head injury'/de OR 'traumatic brain injury'/de OR 'brain contusion'/de OR 'brain concussion'/de OR 'pediatric traumatic brain injury'/de	293809
	2	'brain injur*':ti,ab,kw OR 'head injur*':ti,ab,kw OR 'head trauma*':ti,ab,kw OR 'cranial trauma*':ti,ab,kw OR 'craniocerebral trauma*':ti,ab,kw OR 'cerebr* injur*':ti,ab,kw OR 'brain trauma*':ti,ab,kw OR 'traumat* brain injur*':ti,ab,kw OR tbi:ti,ab,kw OR 'brain lesion*':ti,ab,kw OR 'cerebral lesion*':ti,ab,kw OR 'cerebellum injur*':ti,ab,kw OR 'brain concussion*':ti,ab,kw OR 'brain contusion*':ti,ab,kw OR 'cerebrum lesion*':ti,ab,kw OR 'intracranial injur*':ti,ab,kw OR 'mild traumatic brain injur*':ti,ab,kw OR 'minor traumatic brain injur*':ti,ab,kw OR 'mild head injur*':ti,ab,kw OR 'minor head injur*':ti,ab,kw OR 'minor head trauma':ti,ab,kw OR mtbi:ti,ab,kw OR 'cerebral concussion':ti,ab,kw OR commotio:ti,ab,kw	228641
	3	#1 OR #2	355678
Biomarkers	4	'glial fibrillary acidic protein'/de OR 'ubiquitin thiolesterase'/de OR 'ubiquitin carboxy terminal hydrolase 1'/de OR 'uchl1 protein human'/de OR 'protein s100b'/de OR 'tau protein'/de OR 'microrna'/exp OR 'myelin basic protein'/de OR 'fatty acid binding protein'/exp	382309
	5	s100b:ti,ab,kw OR 's100 b':ti,ab,kw OR 's 100b':ti,ab,kw OR 's100beta':ti,ab,kw OR 's100 beta':ti,ab,kw OR 's 100beta':ti,ab,kw OR 's100 calcium-binding protein b':ti,ab,kw OR 's100 calcium-binding protein beta':ti,ab,kw OR 's100 subunit beta':ti,ab,kw OR 'protein s100beta':ti,ab,kw OR 's 100 b protein':ti,ab,kw OR 's 100 calcium binding protein beta subunit':ti,ab,kw OR 's100 calcium binding protein b':ti,ab,kw OR 's100 calcium binding protein beta subunit':ti,ab,kw OR 's100 protein beta subunit':ti,ab,kw OR 's100beta protein':ti,ab,kw OR gfap:ti,ab,kw OR gfa:ti,ab,kw OR 'gfa protein':ti,ab,kw OR 'glia fibril acidic protein':ti,ab,kw OR 'glia fibril acid protein':ti,ab,kw OR 'glia fibrillary acidic protein':ti,ab,kw OR 'glia fibrillary acid protein':ti,ab,kw OR 'glial acidic fibrillary protein':ti,ab,kw OR 'glial fibrillary acid protein':ti,ab,kw OR 'glial fibrillary acidic protein':ti,ab,kw OR 'glia filament protein':ti,ab,kw OR 'glial fibrillary protein':ti,ab,kw OR 'glial filament protein':ti,ab,kw OR 'protein gfa':ti,ab,kw OR 'uchl 1':ti,ab,kw OR uchl1:ti,ab,kw OR 'uch l1':ti,ab,kw OR 'ubiquitin c-terminal hydrolase':ti,ab,kw OR 'ubiquitin c-terminal esterase':ti,ab,kw OR 'ubiquitin thiolesterase':ti,ab,kw OR 'ubiquitin c terminal thiolester hydrolase':ti,ab,kw OR 'ubiquitin carboxy terminal esterase':ti,ab,kw OR 'ubiquitin carboxy terminal hydrolase':ti,ab,kw OR 'ubiquitin carboxyl terminal hydrolase':ti,ab,kw OR 'ubiquitin carboxyl terminal esterase':ti,ab,kw OR 'ubiquitin carboxyterminal hydrolase':ti,ab,kw OR nfl:ti,ab,kw OR 'nf l':ti,ab,kw OR nefl:ti,ab,kw OR nfm:ti,ab,kw OR 'nf m':ti,ab,kw OR nefm:ti,ab,kw OR 'neurofilament protein':ti,ab,kw OR 'neurofilament light':ti,ab,kw OR 'neurofilament medium':ti,ab,kw OR tau:ti,ab,kw OR mirna*:ti,ab,kw OR microrna*:ti,ab,kw OR 'micro rna*':ti,ab,kw OR nse:ti,ab,kw OR 'neuron-specific enolase':ti,ab,kw OR 'myelin basic protein':ti,ab,kw OR mbp:ti,ab,kw OR 'h fabp':ti,ab,kw OR 'heart fatty acid binding protein':ti,ab,kw OR 'heart type acid binding protein':ti,ab,kw OR 'heart specific fatty acid binding protein':ti,ab,kw OR 'muscle fatty acid binding protein':ti,ab,kw	386895
	6	#4 OR #5	493849
Children	7	'adolescence'/exp OR 'adolescent'/exp OR 'child'/exp OR 'infant'/exp	4732524
	8	adolescen*:ab,kw,ti OR babies:ab,kw,ti OR baby:ab,kw,ti OR boy:ab,kw,ti OR boys:ab,kw,ti OR boyhood:ab,kw,ti OR girlhood:ab,kw,ti OR child*:ab,kw,ti OR girl$:ab,kw,ti OR infan*:ab,kw,ti OR juvenil*:ab,kw,ti OR juvenile*:ab,kw,ti OR kid:ab,kw,ti OR kids:ab,kw,ti OR minor*:ab,kw,ti OR neonat*:ab,kw,ti OR 'neo nat*':ab,kw,ti OR newborn*:ab,kw,ti OR 'new born*':ab,kw,ti OR paediatric*:ab,kw,ti OR peadiatric*:ab,kw,ti OR pediatric*:ab,kw,ti OR perinat*:ab,kw,ti OR preschool*:ab,kw,ti OR puber*:ab,kw,ti OR pubescen*:ab,kw,ti OR school:ab,kw,ti OR 'school child*':ab,kw,ti OR school*:ab,kw,ti OR schoolchild*:ab,kw,ti OR teen*:ab,kw,ti OR toddler$:ab,kw,ti OR underage$:ab,kw,ti OR youth*:ab,kw,ti	4888836
	9	#7 OR #8	6570163
Computed tomography	10	'x-ray computed tomography'/de OR 'dual energy computed tomography'/de OR 'photon counting computed tomography'/de	120769
	11	tomograph*:ti,ab,kw OR 'ct x ray*':ti,ab,kw OR 'cine ct':ti,ab,kw OR 'ct scan*':ti,ab,kw OR 'ctt scan*':ti,ab,kw OR 'cat scan':ti,ab,kw OR 'cat scan*':ti,ab,kw OR 'catting':ti,ab,kw OR 'x ray ct':ti,ab,kw OR 'x rays ct':ti,ab,kw OR 'emi scan':ti,ab,kw OR 'computerised axial tomogram*':ti,ab,kw OR 'computerized axial tomogram*':ti,ab,kw OR 'computerized tomogram*':ti,ab,kw OR 'zonograph*':ti,ab,kw OR ct:ti,ab,kw OR cct:ti,ab,kw OR 'cranial computed tomograph*':ti,ab,kw	1360313
	12	#10 OR #11	1399565
Combined sets	13	#3 AND #6 AND #9 AND #12	300
	14	#3 AND #6 AND #9 AND #12 AND ([english]/lim OR [swedish]/lim)	282
	15	#14 NOT 'conference abstract'/it	224

Field Codes: /de: Emtree term; /exp: Exploded Emtree term; ab: Abstract; kw: Author Keyword; ti: Title.

Database: Cochrane Library
Host: Wiley
Date searched: 2025-05-28
Limits applied: publications in English language

Concept	#	Search	Results
Traumatic brain injury	1	MeSH descriptor: [Head Injuries, Closed] explode all trees	805
	2	MeSH descriptor: [Brain Injuries] explode all trees	3816
	3	MeSH descriptor: [Brain Injuries, Traumatic] this term only	1334
	4	MeSH descriptor: [Brain Concussion] this term only	618
	5	MeSH descriptor: [Brain Contusion] this term only	12
	6	MeSH descriptor: [Craniocerebral Trauma] this term only	452
	7	(brain NEXT injur* or head NEXT injur* or head NEXT trauma* or cranial NEXT trauma* or craniocerebral NEXT trauma* or cerebral NEXT injur* or brain NEXT trauma* or traumatic NEXT brain NEXT injur* or TBI or brain NEXT lesion* or cerebral NEXT lesion* or cerebellum NEXT injur* or brain NEXT concussion* or brain NEXT contusion* or cerebrum NEXT lesion* or intracranial NEXT injur* or mild NEXT traumatic NEXT brain NEXT injur* or minor NEXT traumatic NEXT brain NEXT injur* or mild NEXT head NEXT injur* or minor NEXT head NEXT injur* or "minor head trauma" or mTBI or "cerebral concussion" or commotio):ti,ab,kw	12782
	8	{OR #1-#7}	12866
Biomarkers	9	MeSH descriptor: [Glial Fibrillary Acidic Protein] this term only	51
	10	MeSH descriptor: [Ubiquitin Thiolesterase] this term only	26
	11	MeSH descriptor: [S100 Calcium Binding Protein beta Subunit] this term only	175
	12	MeSH descriptor: [Neurofilament Proteins] this term only	86
	13	MeSH descriptor: [tau Proteins] this term only	201
	14	MeSH descriptor: [MicroRNAs] explode all trees	566
	15	MeSH descriptor: [Myelin Basic Protein] this term only	44
	16	MeSH descriptor: [Fatty Acid-Binding Proteins] explode all trees	171
	17	(UCHL1 protein, human)	22
	18	(S100B or "S100 B" or "S 100B" or "S100beta" or "S100 beta" or "S 100beta" or "S100 calcium-binding protein B" or "S100 calcium-binding protein beta" or "S100 subunit beta" or "protein S100beta" or "S 100 B protein" or "S 100 calcium binding protein beta subunit" or "S100 calcium binding protein B" or "S100 calcium binding protein beta subunit" or "S100 protein beta subunit" or "S100beta protein" or GFAP or GFA or "gfa protein" or "glia fibril acidic protein" or "glia fibril acid protein" or "glia fibrillary acidic protein" or "glia fibrillary acid protein" or "glial acidic fibrillary protein" or "glial fibrillary acid protein" or "glial fibrillary acidic protein" or "glia filament protein" or "glial filament protein" or " glial fibrillary protein" or "glial filament protein" or "protein gfa" or UCHL-1 or UCHL1 or UCH-L1 or "ubiquitin c-terminal hydrolase" or "ubiquitin c-terminal esterase" or "ubiquitin thiolesterase" or "ubiquitin c terminal thiolester hydrolase" or "ubiquitin carboxy terminal esterase" or "ubiquitin carboxy terminal hydrolase" or "ubiquitin carboxyl terminal hydrolase" or "ubiquitin carboxyl terminal esterase" or "ubiquitin carboxyterminal hydrolase" or NFL or NF-L or "NF L" or NEFL or NFM or NF-M or NEFM or "neurofilament protein" or "neurofilament light" or "neurofilament medium" or tau or miRNA* or "micro RNA" or "micro RNAs" or microRNA* or NSE or "neuron-specific enolase" or mbp or "myelin basic protein" or H-FABP or "heart fatty acid binding protein" or "heart type acid binding protein" or "heart specific fatty acid binding protein" or "muscle fatty acid binding protein"):ti,ab,kw	11952
	19	{OR #9-#18}	12105
Children	20	MeSH descriptor: [Adolescent] explode all trees	136477
	21	MeSH descriptor: [Child] explode all trees	81919
	22	MeSH descriptor: [Infant] explode all trees	45528
	23	(adolescen* or babies or baby or boy or boys or boyhood or girlhood or child* or girl* or infan* or juvenil* or kid or kids or minor* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or underage* or under-age* or youth*):ti,ab,kw	426056
	24	[20-#23]	426056
Computed tomography	25	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	8786
	26	(tomograph* or "ct x ray" or "ct x rays" or "cine ct" or "ct scan" or "ctt scan" or "ct scans" or "ctt scans" or "cat scan" or "cat scans" or "catting" or "x ray ct" or "x rays ct" or "emi scan" or computerised NEXT axial NEXT tomogram* or computerized NEXT axial NEXT tomogram* or computerized NEXT tomogram* or zonograph* or CT or CCT or cranial NEXT computed NEXT tomograph*):ti,ab,kw	107036
	27	#25 or #26	107040
Combined sets	28	#8 AND #19 and #24 and #27	25
	29	#8 AND #19 and #24 and #27 (limited to English language)	24

Field Codes: /MeSH descriptor: [] explode all trees: Exploderad Mesh-term; MeSH descriptor: [] this term only: unexplode Mesh-term; ab: Abstract; kw: Keywords; ti: Title

Appendix 2 Excluded studies and reason for exclusion

	Year	Publication	Reason for exclusion
1	2025	Chiollaz A-C, Pouillard V, Seiler M, Habre C, Romano F, Ritter Schenck C, et al. Evaluating NfL and NTproBNP as predictive biomarkers of intracranial injuries after mild traumatic brain injury in children presenting to emergency departments. Frontiers in neurology 2025; 16: 1518776. doi:https://dx.doi.org/10.3389/fneur.2025.1518776	No data No data on biomarkers vs CT
2		Ladang A, Vavoulis G, Trifonidi I, Calluy E, Karagianni K, Mitropoulos A, et al. Increased specificity of the "GFAP/UCH-L1" mTBI rule-out test by age dependent cut-offs. Clinical chemistry and laboratory medicine 2025; 63: 995-1003. doi:https://dx.doi.org/10.1515/cclm-2024-1034	Wrong population All >18 yrs
3		Puravet A, Oris C, Pereira B, Kahouadji S, Gonzalo P, Masson D, et al. Serum GFAP and UCH-L1 for the identification of clinically important traumatic brain injury in children in France: a diagnostic accuracy substudy. The Lancet Child & adolescent health 2025; 9: 47-56. doi:https://dx.doi.org/10.1016/S2352-4642(24)00295-5	No data 86 patients had CT but no data on biomarkers in this group
4	2024	Bouvier D, Cantais A, Laspougeas A, Lorton F, Plenier Y, Cottier M, et al. Serum S100B Level in the Management of Pediatric Minor Head Trauma: A Randomized Clinical Trial. JAMA network open 2024; 7: e242366. doi:https://dx.doi.org/10.1001/jamanetworkopen.2024.2366	Wrong study design RCT for evaluating effectiveness of S100B for reducing CT
5		Mannix R, Borglund E, Monashefsky A, Master C, Corwin D, Badawy M, et al. Age-Dependent Differences in Blood Levels of Glial Fibrillary Acidic Protein but Not Ubiquitin Carboxy-Terminal Hydrolase L1 in Children. Neurology 2024; 103: e209651. doi:https://dx.doi.org/10.1212/WNL.0000000000209651	Wrong population No TBI
6		Menditto VG, Moretti M, Babini L, Mattioli A, Giuliani AR, Fratini M, et al. Minor head injury in anticoagulated patients: performance of biomarkers S100B, NSE, GFAP, UCH-L1 and Alinity TBI in the detection of intracranial injury. A prospective observational study. Clinical chemistry and laboratory medicine 2024; 62: 1376-82. doi:https://dx.doi.org/10.1515/cclm-2023-1169	Wrong population Anticoagulated patients >18 yrs
7		Puccio AM, Yue JK, Korley FK, Okonkwo DO, Diaz-Arrastia R, Yuh EL, et al. Diagnostic Utility of Glial Fibrillary Acidic Protein Beyond 12 Hours After Traumatic Brain Injury: A TRACK-TBI Study. Journal of Neurotrauma 2024; 41: 1353-63. doi:https://10.1089/neu.2023.0186	Wrong population No data on <18 yrs
8		Trnka S, Stejskal P, Jablonsky J, Krahulik D, Pohlodek D, Hrabalek L. S100B protein as a biomarker and predictor in traumatic brain injury. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia 2024; 168: 288-94. doi:https://dx.doi.org/10.5507/bp.2023.025	Wrong population No data on <18 yrs
9	2023	Blackwell LS, Wali B, Xiang Y, Alawieh A, Sayeed I, Reisner A. Prognostic Value of Plasma Biomarkers S100B and Osteopontin in Pediatric TBI: A Prospective Analysis Evaluating Acute and 6-Month Outcomes after Mild to Severe TBI. Biomedicines 2023; 11. doi:https://dx.doi.org/10.3390/biomedicines11082167	No data* No outcome data for GCS 14-15 separately
10		Gardner RC, Puccio AM, Korley FK, Wang KKW, Diaz-Arrastia R, Okonkwo DO, et al. Effects of age and time since injury on traumatic brain injury blood biomarkers: a TRACK-TBI study. Brain communications 2023; 5: fcac316. doi:https://dx.doi.org/10.1093/braincomms/fcac316	Wrong population No data on <18 yrs separately
11		Gök, S., Kilci, A. İ., Gedik, M. S., et al. The usefulness of S100ß protein and fractalkin in predicting traumatic brain injury in pediatric patients with minor head trauma. Intercontinental Journal of Emergency Medicine. 2023, 1, 4,63-66. doi: https://dx.doi.org/10.51271/icjem-0017	No data No data on time for blood draw - head trauma
12		Kelmendi FM, Morina AA, Mekaj AY, Dragusha S, Ahmeti F, Alimehmeti R, et al. Ability of S100B to predict post-concussion syndrome in paediatric patients who present to the emergency department with mild traumatic brain injury. British journal of neurosurgery 2023; 37: 53-8. doi:https://dx.doi.org/10.1080/02688697.2021.1878487	Wrong focus Biomarkers to predict post-concussion syndrome
13	2022	Helmrich IRAR, Czeiter E, Amrein K, Büki A, Lingsma HF, Menon DK, et al. Incremental prognostic value of acute serum biomarkers for functional outcome after traumatic brain injury (CENTER-TBI): an observational cohort study. The Lancet Neurology 2022; 21: 792-802. doi:https://10.1016/S1474-4422(22)00218-6	Wrong focus Prognostic value of biomarkers

14		Korley FK, Jain S, Sun X, Puccio AM, Yue JK, Gardner RC, et al. Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: an observational cohort study. The Lancet Neurology 2022; 21: 803-13. doi:https://10.1016/S1474-4422(22)00256-3	Wrong population No data on <18 yrs separately
15		Papa L, Rosenthal K, Cook L, Caire M, Thundiyil JG, Ladde JG, et al. Concussion severity and functional outcome using biomarkers in children and youth involved in organized sports, recreational activities and non-sport related incidents. Brain injury 2022; 36: 939-47. doi:https://dx.doi.org/10.1080/02699052.2022.2106383	No data No data on <18 yrs separately
16		Ryan E, Kelly L, Stacey C, Duff E, Huggard D, Leonard A, et al. Traumatic Brain Injury in Children: Glial fibrillary Acidic Protein and Clinical Outcomes. Pediatr Emerg Care 2022; 38: e1139-e42. doi:https://10.1097/PEC.0000000000002527	No data No data on biomarkers vs CT outcome
17		Whitehouse DP, Monteiro M, Czeiter E, Vyvere TV, Valerio F, Ye Z, et al. Relationship of admission blood proteomic biomarkers levels to lesion type and lesion burden in traumatic brain injury: A CENTER-TBI study. eBioMedicine 2022; 75. doi:https://10.1016/j.ebiom.2021.103777	Wrong population No data on <18 yrs separately
18	2021	Blais Lécuyer J, Mercier É, Tardif PA, Archambault PM, Chauny JM, Berthelot S, et al. S100B protein level for the detection of clinically significant intracranial haemorrhage in patients with mild traumatic brain injury: A subanalysis of a prospective cohort study. Emergency Medicine Journal 2021; 38: 285-9. doi:https://10.1136/emermed-2020-209583.	Wrong population No data on <18 yrs separately
19		Lorton F, Simon-Pimmel J, Masson D, Launay E, Gras-Le Guen C, Scherdel P. Impact of routine S100B protein assay on CT scan use in children with mild traumatic brain injury. Clinical chemistry and laboratory medicine 2021; 59: 875-82. doi:https://dx.doi.org/10.1515/cclm-2020-1293	Wrong study design Before-after study; impact of PECARN rules incl S100B on CT use
20		Massaeli M, Nava AO, Hejripour Rafsanjani SZ, Bagherzadeh MB, Shahabian M. Diagnostic value of neuron-specific enolase in patients with traumatic brain injury referring to emergency departments in 2015-2016. Journal of Kerman University of Medical Sciences 2021; 28: 319-29. doi:https://10.22062/JKMU.2021.91675	Wrong population No data on <18 yrs separately
21	2020	Forouzan A, Motamed H, Delirrooyfard A, Zallaghi S. Serum Cleaved Tau Protein and Clinical Outcome in Patients with Minor Head Trauma. Open access emergency medicine : OAEM 2020; 12: 7-12. doi:https://dx.doi.org/10.2147/OAEM.S217424	Wrong population No data on <18 yrs separately
22		Gao N, Zhang-Brotzge X, Wali B, Sayeed I, Chern JJ, Blackwell LS, et al. Plasma osteopontin may predict neuroinflammation and the severity of pediatric traumatic brain injury. J Cereb Blood Flow Metab 2020; 40: 35-43. doi:https://10.1177/0271678X19836412	No data* No outcome data for GCS 14-15 separately
23		Lewis JM, Dhawan S, Obirieze AC, Sarno B, Akers J, Heller MJ, et al. Plasma Biomarker for Post-concussive Syndrome: A Pilot Study Using an Alternating Current Electro-Kinetic Platform. Frontiers in neurology 2020; 11: 685. doi:https://dx.doi.org/10.3389/fneur.2020.00685	Wrong population No data on <18 yrs
24		Tylicka M, Matuszczak E, Hermanowicz A, Debek W, Karpinska M, Kaminska J, et al. BDNF and IL-8, But Not UCHL-1 and IL-11, Are Markers of Brain Injury in Children Caused by Mild Head Trauma. Brain Sci 2020; 10. doi:https://10.3390/brainsci10100665	No data No data on CT
25	2019	Cevik S, Ozgenc MM, Guneyk A, Evran S, Akkaya E, Calis F, et al. NRGN, S100B and GFAP levels are significantly increased in patients with structural lesions resulting from mild traumatic brain injuries. Clinical neurology and neurosurgery 2019; 183: 105380. doi:https://dx.doi.org/10.1016/j.clineuro.2019.105380	Wrong population No data on <18 yrs separately
26		Mahan MY, Thorpe M, Ahmadi A, Abdallah T, Casey H, Sturtevant D, et al. Glial Fibrillary Acidic Protein (GFAP) Outperforms S100 Calcium-Binding Protein B (S100B) and Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) as Predictor for Positive Computed Tomography of the Head in Trauma Subjects. World neurosurgery 2019; 128: e434-e44. doi:https://dx.doi.org/10.1016/j.wneu.2019.04.170	Wrong population No data on <18 yrs
27		Parkin GM, Clarke C, Takagi M, Hearps S, Babl FE, Davis GA, et al. Plasma Tumor Necrosis Factor Alpha Is a Predictor of Persisting Symptoms Post-Concussion in Children. Journal of neurotrauma 2019; 36: 1768-75. doi:https://dx.doi.org/10.1089/neu.2018.6042	Wrong focus Biomarkers and post-concussion symptoms
28		Roumpf SK, Welch JL. Can S100B Serum Biomarker Testing Reduce Head Computed Tomography Scanning in Children With Mild Traumatic Brain Injury? Annals of emergency medicine 2019; 73: 456-8. doi:https://dx.doi.org/10.1016/j.annemergmed.2018.10.012	Wrong publication type Editorial / clinical synopsis
29		Stukas S, Higgins V, Frndova H, Gill J, Hubara E, Guerguerian A-M, et al. Characterisation of serum total tau following paediatric traumatic brain injury: a case-control study. The Lancet Child & adolescent health 2019; 3: 558-67. doi:https://dx.doi.org/10.1016/S2352-4642(19)30194-4	Wrong study design Case-control study
30	2018	Aydin I, Algin A, Poyraz MK, Yumrutas O. Diagnostic value of serum glial fibrillary acidic protein and S100B serum levels in emergency medicine patients with traumatic versus nontraumatic intracerebral hemorrhage. Nigerian journal of clinical practice 2018; 21: 1645-50. doi:https://dx.doi.org/10.4103/njcp.njcp_431_17	Wrong population No data on <18 yrs separately

31		Delefortrie Q, Lejeune F, Kerzmann B, Levy R, Adam J-F, Sottiaux T, et al. Evaluation of the Roche R Elecsys and the Diasorin R Liaison S100 kits in the management of mild head injury in the emergency room. Clinical biochemistry 2018; 52: 123-30. doi:https://dx.doi.org/10.1016/j.clinbiochem.2017.11.004	No data No data on biomarkers vs CT
32		Dickens AM, Posti JP, Takala RSK, Ala-Seppala H, Mattila I, Coles JP, et al. Serum Metabolites Associated with Computed Tomography Findings after Traumatic Brain Injury. Journal of neurotrauma 2018; 35: 2673-83. doi:https://dx.doi.org/10.1089/neu.2017.5272	Wrong population No data on <18 yrs
33		Kelmendi FM, Morina AA, Mekaj AY, Blyta A, Alimehmeti R, Dragusha S, et al. Serum S100B Levels Can Predict Computed Tomography Findings in Paediatric Patients with Mild Head Injury. BioMed research international 2018; 6954045. doi:https://dx.doi.org/10.1155/2018/6954045	No data No data on sensitivity / specificity
34		Langness S, Ward E, Halbach J, Lizardo R, Davenport K, Bickler S, et al. Plasma D-dimer safely reduces unnecessary CT scans obtained in the evaluation of pediatric head trauma. J Pediatr Surg 2018; 53: 752-7. doi:https://10.1016/j.jpedsurg.2017.08.017	No data Outcome of biomarker vs ciTBI (not vs CT)
35		Park SH, Hwang SK. Prognostic Value of Serum Levels of S100 Calcium-Binding Protein B, Neuron-Specific Enolase, and Interleukin-6 in Pediatric Patients with Traumatic Brain Injury. World Neurosurg 2018; 118: e534-e42. doi:https://10.1016/j.wneu.2018.06.234	Wrong focus Prognostic value of biomarkers
36	2017	Papa L, Mittal MK, Ramirez J, Silvestri S, Giordano P, Braga CF, et al. Neuronal Biomarker Ubiquitin C-Terminal Hydrolase Detects Traumatic Intracranial Lesions on Computed Tomography in Children and Youth with Mild Traumatic Brain Injury. Journal of neurotrauma 2017; 34: 2132-40. doi:https://dx.doi.org/10.1089/neu.2016.4806	No data No data on <18 yrs and GCS 14-15 separately
37		Peters ME, Rao V, Bechtold KT, Roy D, Sair HI, Leoutsakos J-M, et al. Head injury serum markers for assessing response to trauma: Design of the HeadSMART study. Brain injury 2017; 31: 370-8. doi:https://dx.doi.org/10.1080/02699052.2016.1231344	Wrong population All >18 yrs
38		Li, Q. and Zhou, Q. Relationship between CT features and serum gfAP, NSE and S100B protein in patients with severe traumatic brain injury. Biomedical Research (India). 2017, 28, 22,9926-9929.	Wrong population No data on <18 yrs separately
39	2016	Bouvier D, Duret T, Rouzaire P, Jabaudon M, Rouzaire M, Nourrisson C, et al. Preanalytical, analytical, gestational and pediatric aspects of the S100B immuno-assays. Clinical chemistry and laboratory medicine 2016; 54: 833-42. doi:https://dx.doi.org/10.1515/cclm-2015-0771	Wrong focus S100B in healthy individuals
40		Linsenmaier U, Wirth S, Kanz K-G, Geyer LL. Imaging minor head injury (MHI) in emergency radiology: MRI highlights additional intracranial findings after measurement of trauma biomarker S-100B in patients with normal CCT. The British journal of radiology 2016; 89: 20150827. doi:https://dx.doi.org/10.1259/bjr.20150827	Wrong population No data on <18 yrs
41		Manzano S, Holzinger IB, Kellenberger CJ, Lacroix L, Klima-Lange D, Hersberger M, et al. Diagnostic performance of S100B protein serum measurement in detecting intracranial injury in children with mild head trauma. Emergency medicine journal : EMJ 2016; 33: 42-6. doi:https://dx.doi.org/10.1136/emermed-2014-204513	No data* No outcome data for GCS 14-15 separately
42		Mondello S, Kobeissy F, Vestri A, Hayes RL, Kochanek PM, Berger RP. Serum Concentrations of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein after Pediatric Traumatic Brain Injury. Scientific reports 2016; 6: 28203. doi:https://dx.doi.org/10.1038/srep28203	No data* No outcome data for GCS 14-15 separately
43		Papa L, Brophy GM, Welch RD, Lewis LM, Braga CF, Tan CN, et al. Time Course and Diagnostic Accuracy of Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 in a Large Cohort of Trauma Patients With and Without Mild Traumatic Brain Injury. JAMA neurology 2016; 73: 551-60. doi:https://dx.doi.org/10.1001/jamaneurol.2016.0039	Wrong population Age >18 yrs
44		Papa L, Mittal MK, Ramirez J, Ramia M, Kirby S, Silvestri S, et al. In Children and Youth with Mild and Moderate Traumatic Brain Injury, Glial Fibrillary Acidic Protein Out-Performs S100beta in Detecting Traumatic Intracranial Lesions on Computed Tomography. Journal of neurotrauma 2016; 33: 58-64. doi:https://dx.doi.org/10.1089/neu.2015.3869	No data No data on <18 yrs and GCS 14-15 separately
45		Welch RD, Ayaz SI, Lewis LM, Unden J, Chen JY, Mika VH, et al. Ability of Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase-L1, and S100B To Differentiate Normal and Abnormal Head Computed Tomography Findings in Patients with Suspected Mild or Moderate Traumatic Brain Injury. Journal of neurotrauma 2016; 33: 203-14. doi:https://dx.doi.org/10.1089/neu.2015.4149	Wrong population No data on <18 yrs
46		Rhine T, Babcock L, Zhang N, Leach J, Wade SL. Are UCH-L1 and GFAP promising biomarkers for children with mild traumatic brain injury? Brain Inj 2016; 30: 1231-8. doi:https://10.1080/02699052.2016.1178396	No data No data on CT
47	2015	Heidari K, Asadollahi S, Jamshidian M, Abrishamchi SN, Nouroozi M. Prediction of neuropsychological outcome after mild traumatic brain injury using clinical parameters, serum S100B protein and findings on computed tomography. Brain injury 2015; 29: 33-40. doi:https://dx.doi.org/10.3109/02699052.2014.948068	Wrong focus Prediction of neuropsychological outcome

48		McMahon PJ, Panczykowski DM, Yue JK, Puccio AM, Inoue T, Sorani MD, et al. Measurement of the glial fibrillary acidic protein and its breakdown products GFAP-BDP biomarker for the detection of traumatic brain injury compared to computed tomography and magnetic resonance imaging. Journal of neurotrauma 2015; 32: 527-33. doi:https://dx.doi.org/10.1089/neu.2014.3635	Wrong population No data on <18 yrs
49		Papa L, Zonfrillo MR, Ramirez J, Silvestri S, Giordano P, Braga CF, et al. Performance of Glial Fibrillary Acidic Protein in Detecting Traumatic Intracranial Lesions on Computed Tomography in Children and Youth With Mild Head Trauma. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2015; 22: 1274-82. doi:https://dx.doi.org/10.1111/acem.12795	No data No data on <18 yrs and GCS 14-15 separately
50	2014	Abbasi M, Sajjadi M, Fathi M, Maghsoudi M. Serum S100B Protein as an Outcome Prediction Tool in Emergency Department Patients with Traumatic Brain Injury. Turkish journal of emergency medicine 2014; 14: 147-52. doi:https://dx.doi.org/10.5505/1304.7361.2014.74317	Wrong population No data on <18 yrs
51		Gao W, Lu C, Kochanek PM, Berger RP. Serum amyloid A is increased in children with abusive head trauma: a gel-based proteomic analysis. Pediatr Res 2014; 76: 280-6. doi:https://10.1038/pr.2014.86	Wrong focus Abusive head trauma vs controls
52		Hansen-Schwartz J, Bouchelouche PN. Use of biomarker S100B for traumatic brain damage in the emergency department may change observation strategy. Danish medical journal 2014; 61: A4894. doi:https://ugeskriftet.dk/dmj/use-biomarker-s100b-traumatic-brain-damage-emergency-department-may-change-observation-strategy	Wrong population No data on <18 yrs
53		Laribi S, Kansao J, Borderie D, Collet C, Deschamps P, Ababsa R, et al. S100B blood level measurement to exclude cerebral lesions after minor head injury: the multicenter STIC-S100 French study. Clinical chemistry and laboratory medicine 2014; 52: 527-36. doi:https://dx.doi.org/10.1515/cclm-2013-0621	Wrong population No data on <18 yrs separately
54		Mannix R, Eisenberg M, Berry M, Meehan WP, 3rd, Hayes RL. Serum biomarkers predict acute symptom burden in children after concussion: a preliminary study. J Neurotrauma 2014; 31: 1072-5. doi:https://10.1089/neu.2013.3265	No data No data on CT
55		Papa L, Silvestri S, Brophy GM, Giordano P, Falk JL, Braga CF, et al. GFAP out-performs S100beta in detecting traumatic intracranial lesions on computed tomography in trauma patients with mild traumatic brain injury and those with extracranial lesions. Journal of neurotrauma 2014; 31: 1815-22. doi:https://dx.doi.org/10.1089/neu.2013.3245	Wrong population Age >18 yrs
56		Thelin EP, Nelson DW, Bellander B-M. Secondary peaks of S100B in serum relate to subsequent radiological pathology in traumatic brain injury. Neurocritical care 2014; 20: 217-29. doi:https://dx.doi.org/10.1007/s12028-013-9916-0	Wrong focus Secondary increase of S100B
57		Tylicka M, Matuszczak E, Debek W, Hermanowicz A, Ostrowska H. Circulating proteasome activity following mild head injury in children. Childs Nerv Syst 2014; 30: 1191-6. doi:https://10.1007/s00381-014-2409-4	No data No data on CT
58	2013	Bazarian JJ, Blyth BJ, He H, Mookerjee S, Jones C, Kiechle K, et al. Classification accuracy of serum Apo A-I and S100B for the diagnosis of mild traumatic brain injury and prediction of abnormal initial head computed tomography scan. Journal of neurotrauma 2013; 30: 1747-54. doi:https://dx.doi.org/10.1089/neu.2013.2853	Wrong population No data on <18 yrs
59		Thelin EP, Johannesson L, Nelson D, Bellander B-M. S100B is an important outcome predictor in traumatic brain injury. Journal of neurotrauma 2013; 30: 519-28. doi:https://dx.doi.org/10.1089/neu.2012.2553	Wrong population No data on <18 yrs separately
60	2012	Babcock L, Byczkowski T, Mookerjee S, Bazarian JJ. Ability of S100B to predict severity and cranial CT results in children with TBI. Brain injury 2012; 26: 1372-80. doi:https://dx.doi.org/10.3109/02699052.2012.694565	Wrong study design Secondary analysis
66		Berger RP, Hayes RL, Richichi R, Beers SR, Wang KK. Serum concentrations of ubiquitin C-terminal hydrolase-L1 and alphaII-spectrin breakdown product 145 kDa correlate with outcome after pediatric TBI. J Neurotrauma 2012; 29: 162-7. doi:https://10.1089/neu.2011.1989	No data* No outcome data for GCS 14-15 separately
61		Bouvier D, Fournier M, Dauphin J-B, Amat F, Ughetto S, Labbe A, et al. Serum S100B determination in the management of pediatric mild traumatic brain injury. Clinical chemistry 2012; 58: 1116-22. doi:https://dx.doi.org/10.1373/clinchem.2011.180828	No data* No outcome data for GCS 14-15 separately
62		Cervellin G, Benatti M, Carbucicchio A, Mattei L, Cerasti D, Aloe R, et al. Serum levels of protein S100B predict intracranial lesions in mild head injury. Clinical biochemistry 2012; 45: 408-11. doi:https://dx.doi.org/10.1016/j.clinbiochem.2012.01.006	Wrong population No data on <18 yrs
63		Metting Z, Wilczak N, Rodiger LA, Schaaf JM, van der Naalt J. GFAP and S100B in the acute phase of mild traumatic brain injury. Neurology 2012; 78: 1428-33. doi:https://dx.doi.org/10.1212/WNL.0b013e318253d5c7	Wrong population No data on <18 yrs

64		Papa L, Lewis LM, Silvestri S, Falk JL, Giordano P, Brophy GM, et al. Serum levels of ubiquitin C-terminal hydrolase distinguish mild traumatic brain injury from trauma controls and are elevated in mild and moderate traumatic brain injury patients with intracranial lesions and neurosurgical intervention. The journal of trauma and acute care surgery 2012; 72: 1335-44. doi:https://dx.doi.org/10.1097/TA.0b013e3182491e3d	Wrong population Age >18 yrs
65		Zongo D, Ribereau-Gayon R, Masson F, Laborey M, Contrand B, Salmi LR, et al. S100-B protein as a screening tool for the early assessment of minor head injury. Annals of emergency medicine 2012; 59: 209-18. doi:https://dx.doi.org/10.1016/j.annemergmed.2011.07.027	Wrong population No data on <18 yrs
66		Egea-Guerrero JJ, Revuelto-Rey J, Murillo-Cabezas F, Muñoz-Sánchez MA, Vilches-Arenas A, Sánchez-Linares P, et al. Accuracy of the S100β protein as a marker of brain damage in traumatic brain injury. Brain Injury 2012; 26: 76-82. doi:https://10.3109/02699052.2011.635360	Wrong population No data on <18 yrs separately
67		Sezer AA, Akinci E, Öztürk M, Coşkun F, Yilmaz G, Karakaş A, et al. The role of blood S100B and lactate levels in minor head traumas in children and adults and correlation with brain computerized tomography. Ulusal Travma ve Acil Cerrahi Dergisi 2012; 18: 411-6. doi:https://10.5505/tjtes.2012.76736	Wrong language Turkish
68	2011	Astrand R, Romner B, Lanke J, Unden J. Reference values for venous and capillary S100B in children. Clinica chimica acta; international journal of clinical chemistry 2011; 412: 2190-3. doi:https://dx.doi.org/10.1016/j.cca.2011.08.009	Wrong focus Only healthy children
69		Gonzclez-Mao MC, Reparaz-Andrade A, Del Campo-Perez V, Alvarez-Garcia E, Vara-Perez C, Andrade-Olivie MA. Model predicting survival/exitus after traumatic brain injury: biomarker S100B 24h. Clinical laboratory 2011; 57: 587-97. doi:https://www.clin-lab-publications.com/issue/76	Wrong population No data on <18 yrs separately
70		Muller B, Evangelopoulos DS, Bias K, Wildisen A, Zimmermann H, Exadaktylos AK. Can S-100B serum protein help to save cranial CT resources in a peripheral trauma centre? A study and consensus paper. Emergency medicine journal : EMJ 2011; 28: 938-40. doi:https://dx.doi.org/10.1136/emj.2010.095372	Wrong population No data on <18 yrs
71		Zurek J, Bartlova L, Fedora M. Hyperphosphorylated neurofilament NF-H as a predictor of mortality after brain injury in children. Brain injury 2011; 25: 221-6. doi:https://dx.doi.org/10.3109/02699052.2010.541895	Wrong focus Biomarker as a predictor of mortality
72		Zurek J, Fedora M. Dynamics of glial fibrillary acidic protein during traumatic brain injury in children. The Journal of trauma 2011; 71: 854-9. doi:https://dx.doi.org/10.1097/TA.0b013e3182140c8c	Wrong population GCS <9
73	2010	Chang TP, Nager AL. Pediatric traumatic brain injury: the utility of beta-natriuretic peptide. J Trauma 2010; 68: 1401-5. doi:https://10.1097/TA.0b013e3181bb9a87	No data No GCS distribution presented
74		Guzel A, Karasalihoglu S, Aylanc H, Temizoz O, Hicdonmez T. Validity of serum tau protein levels in pediatric patients with minor head trauma. The American journal of emergency medicine 2010; 28: 399-403. doi:https://dx.doi.org/10.1016/j.ajem.2008.12.025	No data No data on time for blood draw in relation to head trauma
75		Hallen M, Karlsson M, Carlhed R, Hallgren T, Bergenheim M. S-100B in serum and urine after traumatic head injury in children. The Journal of trauma 2010; 69: 284-9. doi:https://dx.doi.org/10.1097/ta.0b013e3181ca060b	No data Pats with neg CT mixed with pats who had no CT
76		Swanson CA, Burns JC, Peterson BM. Low plasma D-dimer concentration predicts the absence of traumatic brain injury in children. The Journal of trauma 2010; 68: 1072-7. doi:https://dx.doi.org/10.1097/TA.0b013e3181d7a6f2	No data Presented data do not add up Inconsistent data
77		Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: comparison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta neurologica Scandinavica 2010; 121: 178-85. doi:https://dx.doi.org/10.1111/j.1600-0404.2009.01196.x	Wrong population No data on <18 yrs separately
78	2009	Bechtel K, Frasure S, Marshall C, Dziura J, Simpson C. Relationship of serum S100B levels and intracranial injury in children with closed head trauma. Pediatrics 2009; 124: e697-704. doi:https://dx.doi.org/10.1542/peds.2008-1493	No data No data on GCS distribution
79		Berger RP, Ta'asan S, Rand A, Lokshin A, Kochanek P. Multiplex assessment of serum biomarker concentrations in well-appearing children with inflicted traumatic brain injury. Pediatr Res 2009; 65: 97-102. doi:https://10.1203/PDR.0b013e31818c7e27	No data Blood sampling mean 26 hrs after trauma
80		Castellani C, Bimbashi P, Ruttenstock E, Sacherer P, Stojakovic T, Weinberg AM. Neuroprotein s-100B -- a useful parameter in paediatric patients with mild traumatic brain injury? Acta paediatrica (Oslo, Norway : 1992) 2009; 98: 1607-12. doi:https://dx.doi.org/10.1111/j.1651-2227.2009.01423.x	No data* No outcome data for GCS 14-15 separately

81		Geyer C, Ulrich A, Grafe G, Stach B, Till H. Diagnostic value of S100B and neuron-specific enolase in mild pediatric traumatic brain injury. J Neurosurg Pediatr 2009; 4: 339-44. doi:https://10.3171/2009.5.PEDS08481	No data No data on biomarkers vs CT
82		Lo T-YM, Jones PA, Minns RA. Pediatric brain trauma outcome prediction using paired serum levels of inflammatory mediators and brain-specific proteins. Journal of neurotrauma 2009; 26: 1479-87. doi:https://dx.doi.org/10.1089/neu.2008-0753	Wrong population GCS 3-13
83		Morochovic R, Racz O, Kitka M, Pingorova S, Cibur P, Tomkova D, et al. Serum S100B protein in early management of patients after mild traumatic brain injury. European journal of neurology 2009; 16: 1112-7. doi:https://dx.doi.org/10.1111/j.1468-1331.2009.02653.x	Wrong population No data on <18 yrs separately
84	2008	Bak HU, Sung WY, Lee JY, et al. The Usefulness of Serum S-100 beta Levels as a Screening Test for Pediatric Minor Head Trauma. J Korean Soc Emerg Med. 2008, 19(2), 185-191. dio:https://www.jksem.org/upload/pdf/18401875.pdf	Wrong language Korean
85		Castellani C, Stojakovic T, Cichocki M, Scharnagl H, Erwa W, Gutmann A, et al. Reference ranges for neuroprotein S-100B: from infants to adolescents. Clinical chemistry and laboratory medicine 2008; 46: 1296-9. doi:https://dx.doi.org/10.1515/CCLM.2008.262	Wrong focus Healthy children only
86		Guzel A, Er U, Tatli M, Aluclu U, Ozkan U, Duzenli Y, et al. Serum neuron-specific enolase as a predictor of short-term outcome and its correlation with Glasgow Coma Scale in traumatic brain injury. Neurosurgical review 2008; 31: 439-5. doi:https://dx.doi.org/10.1007/s10143-008-0148-2	Wrong population No data on <18 yrs separately
87		Pickering A, Carter J, Hanning I, Townend W. Emergency department measurement of urinary S100B in children following head injury: can extracranial injury confound findings? Emergency medicine journal : EMJ 2008; 25: 88-9. doi:https://dx.doi.org/10.1136/emj.2007.046631	Wrong focus Urinary test for S100B
88	2007	Berger RP, Beers SR, Richichi R, Wiesman D, Adelson PD. Serum biomarker concentrations and outcome after pediatric traumatic brain injury. J Neurotrauma 2007; 24: 1793-801. doi:https://10.1089/neu.2007.0316	Wrong focus Correlation biomarkers - Glasgow Outcome Scale
89		Muller K, Townend W, Biasca N, Unden J, Waterloo K, Romner B, et al. S100B serum level predicts computed tomography findings after minor head injury. The Journal of trauma 2007; 62: 1452-6. doi:https://dx.doi.org/10.1097/TA.0b013e318047bfaa	Wrong population No data on <18 yrs separately
90		Piazza O, Storti MP, Cotena S, Stoppa F, Perrotta D, Esposito G, et al. S100B is not a reliable prognostic index in paediatric TBI. Pediatric neurosurgery 2007; 43: 258-64. doi:https://dx.doi.org/10.1159/000103304	Wrong focus S100B as a prognostic test
91	2006	Bazarian JJ, Beck C, Blyth B, von Ahsen N, Hasselblatt M. Impact of creatine kinase correction on the predictive value of S-100B after mild traumatic brain injury. Restorative neurology and neuroscience 2006; 24: 163-72. doi:https://journals.sagepub.com/doi/abs/10.3233/RNN-2006-00342	Wrong focus CK correction and predictive value of S100B
92		Berger RP, Dulani T, Adelson PD, Leventhal JM, Richichi R, Kochanek PM. Identification of inflicted traumatic brain injury in well-appearing infants using serum and cerebrospinal markers: a possible screening tool. Pediatrics 2006; 117: 325-32. doi:https://dx.doi.org/10.1542/peds.2005-0711	Wrong focus Biomarkers for the identification of inflicted TBI
93		Biberthaler P, Linsenmeier U, Pfeifer K-J, Kroetz M, Mussack T, Kanz K-G, et al. Serum S-100B concentration provides additional information fot the indication of computed tomography in patients after minor head injury: a prospective multicenter study. Shock (Augusta, Ga) 2006; 25: 446-53. doi:https://dx.doi.org/10.1097/01.shk.0000209534.61058.35	Wrong population No data on <18 yrs
94		Naeimi ZS, Weinhofer A, Sarahrudi K, Heinz T, Vecsei V. Predictive value of S-100B protein and neuron specific-enolase as markers of traumatic brain damage in clinical use. Brain injury 2006; 20: 463-8. doi:https://dx.doi.org/10.1080/02699050600664418	Wrong population No data on <18 yrs separately
95		Poli-de-Figueiredo LF, Biberthaler P, Simao Filho C, Hauser C, Mutschler W, Jochum M. Measurement of S-100B for risk classification of victims sustaining minor head injury--first pilot study in Brazil. Clinics (Sao Paulo, Brazil) 2006; 61: 41-6. doi:https://dx.doi.org/10.1590/s1807-59322006000100008	Wrong population No data on age
96	2005	Bandyopadhyay S, Hennes H, Gorelick MH, Wells RG, Walsh-Kelly CM. Serum neuron-specific enolase as a predictor of short-term outcome in children with closed traumatic brain injury. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2005; 12: 732-8. doi:https://dx.doi.org/10.1197/j.aem.2005.02.017	No data No data on biomarkers vs CT outcome
98	2004	Stranjalis G, Korfias S, Papapetrou C, Kouyialis A, Boviatsis E, Psachoulia C, et al. Elevated serum S-100B protein as a predictor of failure to short-term return to work or activities after mild head injury. Journal of Neurotrauma 2004; 21: 1070-5. doi:https://10.1089/0897715041651088	Wrong population No data on <18 yrs separately

99	2003	Akhtar JI, Spear RM, Senac MO, Peterson BM, Diaz SM. Detection of traumatic brain injury with magnetic resonance imaging and S-100B protein in children, despite normal computed tomography of the brain. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2003; 4: 322-6. doi:https://dx.doi.org/10.1097/01.PCC.0000075323.47797.B8	Wrong population All children had normal CT
100		Mussack T, Dvorak J, Graf-Baumann T, Jochum M. Serum S-100B protein levels in young amateur soccer players after controlled heading and normal exercise. European journal of medical research 2003; 8: 457-64. https://pubmed.ncbi.nlm.nih.gov/14594652/	Wrong population No data on <18 yrs
101		Spinella PC, Dominguez T, Drott HR, Huh J, McCormick L, Rajendra A, et al. S-100beta protein-serum levels in healthy children and its association with outcome in pediatric traumatic brain injury. Crit Care Med 2003; 31: 939-45. doi:https://10.1097/01.CCM.0000053644.16336.52	No data No data on CT scan
102	2002	Biberthaler P, Mussack T, Wiedemann E, Kanz KG, Mutschler W, Linsenmaier U, et al. Rapid identification of high-risk patients after minor head trauma (MHT) by assessment of S-100B: ascertainment of a cut-off level. European journal of medical research 2002; 7: 164-70. https://pubmed.ncbi.nlm.nih.gov/12010651/	Wrong population No info on age
103		Mussack T, Biberthaler P, Kanz KG, Heckl U, Gruber R, Linsenmaier U, et al. Immediate S-100B and neuron-specific enolase plasma measurements for rapid evaluation of primary brain damage in alcohol-intoxicated, minor head-injured patients. Shock (Augusta, Ga) 2002; 18: 395-400. doi:https://dx.doi.org/10.1097/00024382-200211000-00002	Wrong population No data on <18 yrs
104		Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Kochanek PM. Serum S100B concentrations are increased after closed head injury in children: a preliminary study. J Neurotrauma 2002; 19: 1405-9. doi:https://10.1089/089771502320914633	No data Not all S-100B were within 6 hours
105	2001	Biberthaler P, Mussack T, Wiedemann E, Kanz KG, Koelsch M, Gippner-Steppert C, et al. Evaluation of S-100b as a specific marker for neuronal damage due to minor head trauma. World journal of surgery 2001; 25: 93-7. doi:https://dx.doi.org/10.1007/s002680020370	Wrong population No info on age
106		Herrmann M, Curio N, Jost S, Grubich C, Ebert AD, Fork ML, et al. Release of biochemical markers of damage to neuronal and glial brain tissue is associated with short and long term neuropsychological outcome after traumatic brain injury. Journal of neurology, neurosurgery, and psychiatry 2001; 70: 95-100. doi:https://dx.doi.org/10.1136/jnnp.70.1.95	Wrong population No data on <18 yrs separately
107	2000	Fridriksson T, Kini N, Walsh-Kelly C, Hennes H. Serum neuron-specific enolase as a predictor of intracranial lesions in children with head trauma: a pilot study. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2000; 7: 816-20. doi:https://dx.doi.org/10.1111/j.1553-2712.2000.tb02276.x	No data* No outcome data for GCS 14-15 separately
108		Herrmann M, Jost S, Kutz S, Ebert AD, Kratz T, Wunderlich MT, et al. Temporal profile of release of neurobiochemical markers of brain damage after traumatic brain injury is associated with intracranial pathology as demonstrated in cranial computerized tomography. Journal of neurotrauma 2000; 17: 113-22. doi:https://dx.doi.org/10.1089/neu.2000.17.113	Wrong population No data on <18 yrs separately
109		Mussack T, Biberthaler P, Wiedemann E, Kanz KG, Englert A, Gippner-Steppert C, et al. S-100b as a screening marker of the severity of minor head trauma (MHT)--a pilot study. Acta neurochirurgica Supplement 2000; 76: 393-6. doi:https://dx.doi.org/10.1007/978-3-7091-6346-7_81	Wrong publication type Conference paper
110		Romner B, Ingebrigtsen T, Kongstad P, Borgesen SE. Traumatic brain damage: serum S-100 protein measurements related to neuroradiological findings. J Neurotrauma 2000; 17: 641-7. doi:https://10.1089/089771500415391	Wrong population No data on <18 yrs separately
111	1999	Herrmann M, Curio N, Jost S, Wunderlich MT, Synowitz H, Wallesch CW. Protein S-100B and neuron specific enolase as early neurobiochemical markers of the severity of traumatic brain injury. Restorative Neurology and Neuroscience 1999; 14: 109-14. https://www.embase.com/search/results?subaction=viewrecord&id=L29173191&from=export	Wrong population No data on <18 yrs separately
112	1998	Ergun R, Bostanci U, Akdemir G, Beskonakli E, Kaptanoglu E, Gursoy F, et al. Prognostic value of serum neuron-specific enolase levels after head injury. Neurological research 1998; 20: 418-20. doi:https://dx.doi.org/10.1080/01616412.1998.11740541	Wrong population No data on <18 yrs separately
113	1992	Skogseid, I. M., Nordby, H. K., Urdal, P., et al. Increased serum creatine kinase BB and neuron specific enolase following head injury indicates brain damage. Acta neurochirurgica. 1992, 115, 3-4,106-11.	Wrong population Age >18 yrs

*No data on GCS 14 and 15 separately

Appendix 3 Accuracy and calculated likelihood ratio of positive and negative tests based on data extracted from the study by Chiollaz, and Simon-Pimmel, respectively.

Threshold values for likelihood ratios of positive and negative tests, respectively:
LR (+) >2 is of clinical interest; LR (-) <0.2 is of clinical interest

Table 1 Distribution of patients when sensitivity is set at 100% and specificity 33%, from the study by Chiollaz et al (n=43)

	CT positive	CT negative	Total
S100B pos	7	24	31
S100B neg	0	12	12
Totalt	7	36	43

Sensitivity 7/7 = 1
Specificity 12/36 = 0.33
LR + (7/7) / (24/36) = 1/0.66 = 1.5
LR - (0/7) / (12/36) = 0/0.33 = 0
PPV 7/31 = 23%
NPV 12/12 = 1

Table 2a Distribution of all patients included according to findings presented in Figure 2 in the study by **Simon-Pimmel** (n=109)

	Traumatic brain injury	No traumatic brain injury	Total
S100B pos	13	34	47
S100B neg	4	58	62
Total	17	92	109

Sensitivity 13/17 =0.76
Specificity 58/92 = 0.63
LR + (13/17) / (34/92) = 0.76 / 0.37 = 2.05
LR – (4/17) / (58/92) = 0.24 / 0.63 = 0.38
PPV 13/47 = 0.28
NPV 58/62 = 0.89

Table 2b Distribution of patients in **the PECARN high-risk group** according to findings presented in Figure 2 in the study by Simon-Pimmel et al (n=60)

	Traumatic brain injury	No traumatic brain injury	Total
S100B pos	12	18	30
S100B neg	3	27	30
Total	15	45	60

Sensitivity 12/15 = 0.8
Specificity 27/45 = 0.6
LR + (12/15) / (18/45) = 0.8 / 0.4 = 2
LR – (3/15 / (27/45) = 0.2 / 0.6 = 0.33
PPV 12/30 = 0.4
NPV 27/30 = 0.9

Table 2c Distribution of patients in **the PECARN intermediate-risk group** according to the findings presented in Figure 2 in the study by Simon-Pimmel (n=47)

	Traumatic brain injury	No traumatic brain injury	Total
S100B pos	1	16	17
S100B neg	1	29	30
Total	2	45	47

Sensitivity 1/2 = 0.5
Specificity 29/ 45 = 0.64
LR + (1/2) / (16/45) = 0.5 / 0.35 = 1.4
LR – (1/2) / (29/45) = 0.5 / 0.64 = 0.8
PPV 1/17 = 0.06
NPV 29/30 = 0.97

Table 2d Distribution of patients in the **PECARN low-risk group** according to findings presented in Figure 2 in the study by Simon-Pimmel (n=2)

	Traumatic brain injury	No traumatic brain injury	Total
S100B pos	0	0	0
S100B neg	0	2	2
Total	0	2	2

Sensitivity 0/0 = undefined
Specificity 2/2 = 1
LR + (0/0) / (0/2) = undefined
LR – (0/0) / (2/2) = undefined

Three scenarios based on the findings in the study by Simon-Pimmel

If both the high- and intermediate risk group used S100B, the number of CT scans would be 47, and 4/17 (24%) TBI would be missed (Table 3).

If all patients in the PECARN high-risk group had CT and the intermediate-risk group used S100B, the number of CT scans would be 77 and 1/17 (6%) TBI be missed.

If all patients in the PECARN high-risk group had CT but no patient in the intermediate group had CT, the number of CT scans would be 60 and 2/17 (12%) patients with TBI be missed.

Table 3 Number of CT and proportion of TBI missed based on data from the study by Simon-Pimmel.

High risk group	**Intermediate risk group**	**Number of head CT**	**Proportion of TBI missed**
CT based on S100B	CT based on S100B	47	24%
All had CT	CT based on S100B	77	6%
All had CT	None had CT	60	12%

Appendix 4 Specificity and positive predictive values at prevalence rates of 1/100 and 1/1000 with 100% sensitivity.

A Prevalence of condition 1/100 (eg ciTBI), and specificity 33, 50, 66 and 99%.

Specificity 99%

	CT pos	CT neg	Totalt
Pos lab test	1	1	2
Neg lab test	0	98	98
Total	1	99	100

PPV 1 / 2 = 0.5

Specificity 66%

	CT pos	CT neg	Totalt
Pos lab	1	34	35
Neg lab	0	65	65
Total	1	99	100

PPV = 1/ 35 = 0.03

Specificity 50%

	CT pos	CT neg	Totalt
Pos lab	1	49	50
Neg lab	0	50	50
Total	1	99	100

PPV = 1/50 = 0.02

Specificity 33%

	CT pos	CT neg	Totalt
Pos lab	1	66	67
Neg lab	0	33	33
Total	1	99	100

PPV =1/67 = 0.015

Summary: A better specificity, from 33% to 66%, will increase the PPV from 1/67 (1.5%) to 1/35 (3%). PPV is 50% when the specificity is 99%.

B Prevalence of condition 1/1000 (e.g. need for neurosurgical intervention), and specificity 33, 50, 66 and 99%

Specificity 99%

	CT pos	CT neg	Totalt
Pos lab	1	10	11
Neg lab	0	989	989
Total	1	999	1000

PPV = 1 / 11 = 0.09

Specificity 66%

	CT pos	CT neg	Totalt
Pos lab	1	340	341
Neg lab	0	659	659
Total	1	999	1000

PPV = 1/ 341 = 0.003

Specificity 50%

	CT pos	CT neg	Totalt
Pos lab	1	499	500
Neg lab	0	500	500
Total	1	999	1000

PPV = 1 / 500 = 0.002

Specificity 33%

	CT pos	CT neg	Totalt
Pos lab	1	669	670
Neg lab	0	330	330
Total	1	999	1000

PPV = 1 / 670 = 0.001

Summary: A better specificity, from 33% to 66%, will increase the PPV from 1/670 (1.5‰) to 1/341 (3‰). PPV is 9% when the specificity is 99%.

Conclusion: Given the low prevalence of the condition examined, anything but a very high specificity will lead to a meaningful increase in the positive predictive value.


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