società italiana medicina d'emergenza-urgenza

I Biomarcatori nel Trauma Cranico Lieve

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Conflicts ….

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TBIs range from mild to severe

Classification of TBI severity

Criteria	Mild	Moderate	Severe
N of cases	92-94%	3-4%	1-2%
Positive CT	4-7%	50%	75%
Neurosurgical Intervention	0.5%	15%	30%
Mortality	0.2%	3-4%	>20%
Glasgow Coma Scale (best available score in first 24 hrs)	14–15	9–13	< 9

Mild TBI (a brief change in mental status or consciousness)

Severe TBI (an extended period of unconsciousness or memory loss)

Most TBIs that occur each year are mild, commonly called concussions[2]

TBI, traumatic brain injury

1. O'Neil et al (2012). Complications of mild traumatic brain injury in veterans and military personnel: A Systematic Review. VA-ESP Project #05-225;
2. Centers for Disease Control and Prevention (CDC), National Center for Injury Prevention and Control. Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Atlanta (GA): Centers for Disease Control and Prevention; 2003.

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However, **CT is not 100% sensitive for intracranial complications**[4–6]

C
1. af Geijerstam
et
4. al et al (2008).
Neurol Res 30:974–978.

A Critical Comparison of Clinical Decision Instruments for Computed Tomographic Scanning in Mild Closed Traumatic Brain Injury in Adolescents and Adults

Table 1. Findings used by 7 clinical decision rules for CT scanning in mild traumatic brain injury.

Clinical Finding	Canadian	NCWFNS	New Orleans	NEXUS-II	NICE	Scandinavian
GCS score	<15 At 2 h	<15	<15	Abnormal alertness, behavior	<15 At 2 h	<15
Amnesia	Retrograde >30 min*	Any	Antegrade	—	Retrograde >30 min	Any
Suspected fracture	Open, depressed, basal	Any	Any injury above clavicles	Any	Open, depressed, basal	Basal, depres confirmed
Vomiting	Recurrent	Any	Any	Recurrent	Recurrent	—
Age, y	≥65	—	>60	≥65	≥65†	—
Coagulopathy	—	Any	—	Any	Any†	Any
Focal deficit	—	Any	—	Any	Any	Any
Seizure	—	History	Any	—	Any	Any
LOC	If GCS=14	Any	—	—	—	Any
Visible trauma	—	—	Above clavicles	Scalp hematoma	—	Multiple injuri
Headache	—	Any	Severe	—	—	—
Injury mechanism	Dangerous*†	—	—	—	Dangerous††	—
Intoxication	—	Abuse history	Drug, alcohol	—	—	—
Previous neurosurgery	—	Yes	—	—	—	Shunt

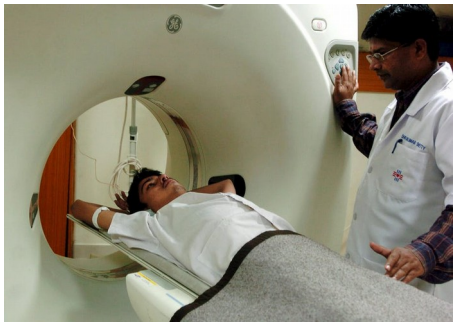
NCWFNS, Neurotraumatology Committee of the World Federation of Neurosurgical Societies; *NICE,* National Institute of Clinical Excellence; —, indicates the item not considered an indication for CT scanning by author(s) of the rule; *LOC,* loss of consciousness.

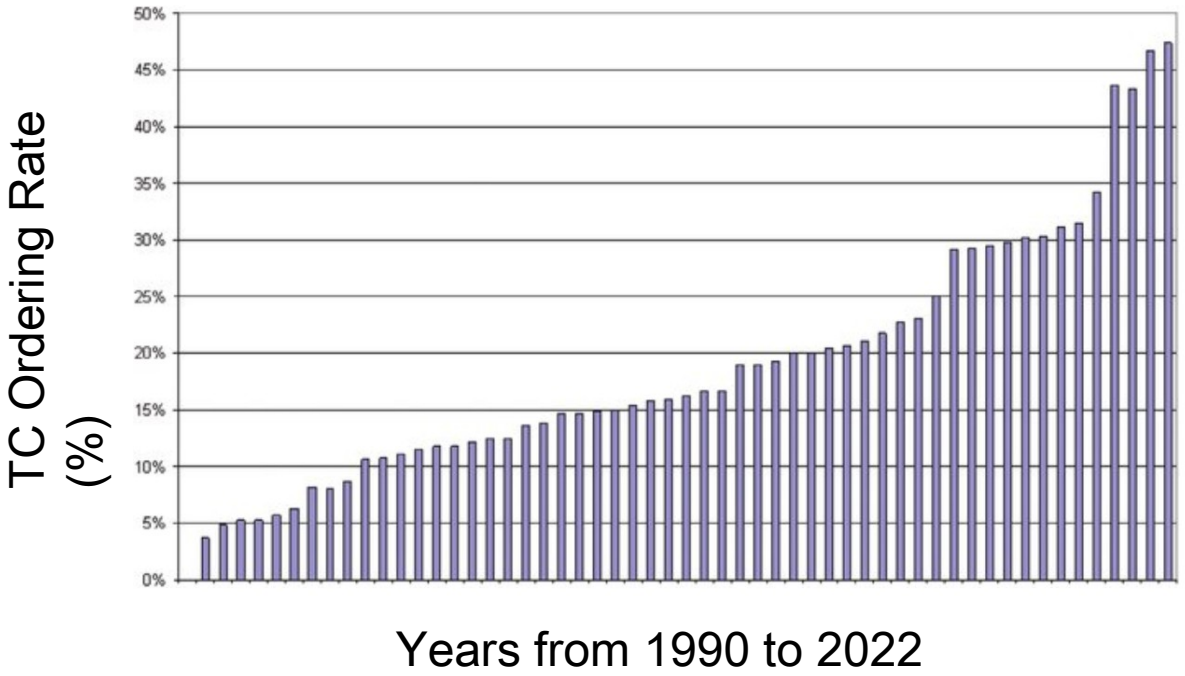
*Used to determine medium risk for the Canadian Rule.

†CT scan only if also loss of consciousness or any amnesia.

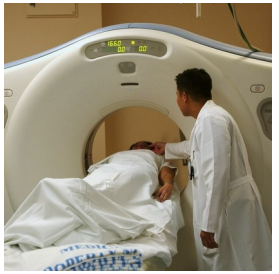
†Dangerous injury mechanism=ejected from motor vehicle, pedestrian struck by motor vehicle, fall of >3 feet or 5 steps.

Head CT scan for TBI in the last decades

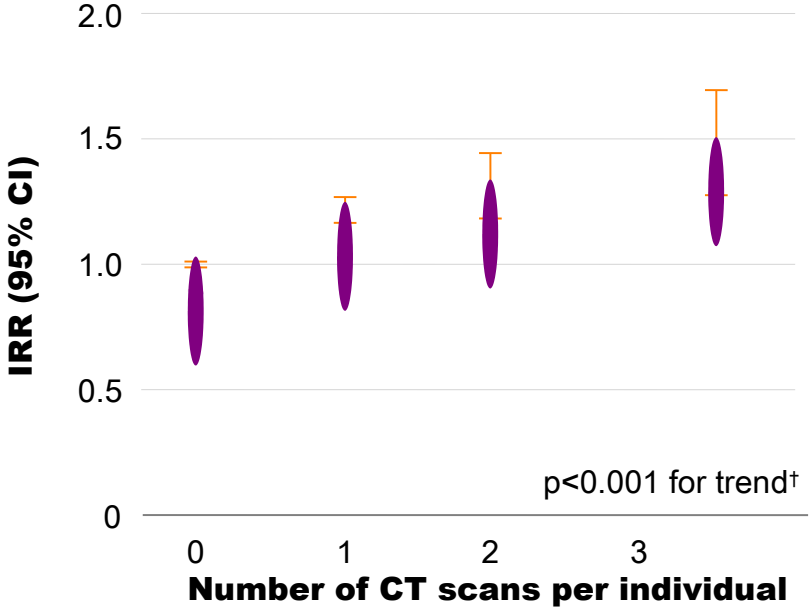




Ionizing Radiation increased risk of Cancer: in Children more than **Adults**

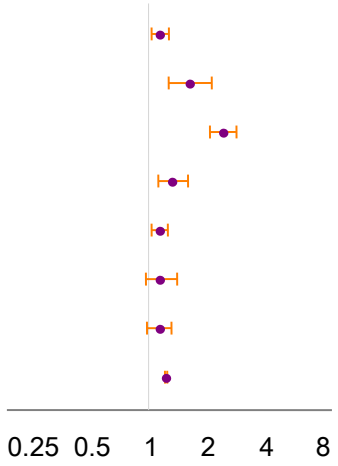


Incidence rate ratios (IRR) for all cancer types according to number of CT scans (n=680,211)*



IRRs for exposed vs unexposed in subset of patients with brain CT scans (n=404,105)*

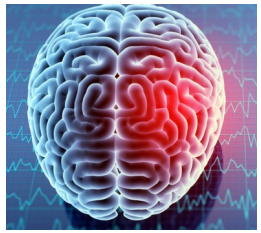
Cancer type	No. of cancers in exposed	IRR (95% CI)	IRR
Melanoma	511		1.14
Soft tissue	69		1.64
Brain	210		2.44
Thyroid	155		1.33
Other solid cancers	633		1.13
Leuk./myelodysplasias	149		1.16
Other lymphoid/hemato	237		1.13
All cancers	1964		1.23



Future CT scans should be limited to situations where there is a definite clinical indication, with every scan optimized to provide a diagnostic CT image at the lowest possible radiation dose

Data are for 10.9 million children and adolescents (0–19 years old), of which 680,211 had a CT scan. * Based on a one-year lag period.
† Overall cancer incidence was 24% greater for exposed vs unexposed (IRR 1.24; 95% CI 1.20–1.29). The IRR increased by 0.16 for each additional scan.
Mathews et al (2013). BMJ 346:f2360.

Unmet Needs in Mild TBI



CT is costly, not always available[1] and exposes patient to high radiation doses[2]

Optimal clinical decision rule for initial CT scan is still a matter of debate[1]

- Need for rapid assessment of injury and increased ED efficiency

Indicators needed to avoid unnecessary CT scans

- CT reveals clinically relevant lesions in <10% of cases
- Biomarkers and alternative imaging tools are needed to
  - risk stratify patients (identify those safe to send home)
  - identify patients at risk of deterioration (monitoring)

Approved therapies needed for targeted treatment of TBI[3]

- Current therapies range from medical management alone with frequent neurological exams, to invasive intracranial monitoring, and as a last resort to radical decompressive surgical interventions

CT, computed tomography; ED. emergency department; TBI, traumatic brain injury

1. Zongo et al (2012). Ann Emerg Med 59:209–218; 2. Smith-Bindman (2010). N Engl J Med 363:1–4; 3. Pearce et al (2012). Lancet 380:499–505;
3. Galgano et al (2017). Cell Transplant 26:1118–1130.

Over the last decades, an increasing effort to find TBI-specific biomarker candidates

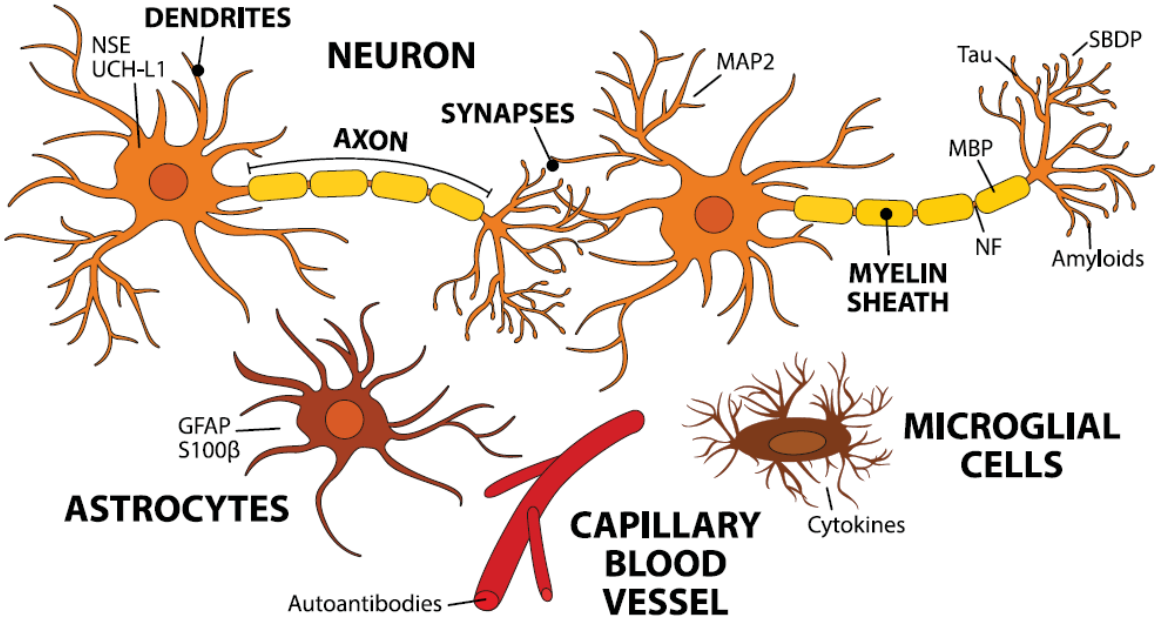
Novel biomarkers may help to better understand the disease mechanism to:

TBI, traumatic brain injury

Kobeissy and Stevens, Jr. (eds.), Neuroproteomics: Methods and Protocols, Methods in Molecular Biology, vol. 1598, DOI 10.1007/978-1-4939-6952-4_3; Chapter 3.

Biomarkers & Investigations in TBI

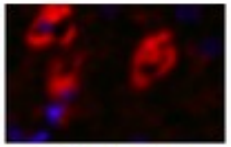
Possible cellular origin of biomarkers associated with TBI pathology



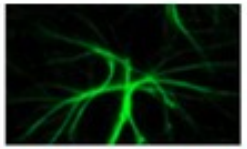
Biomarkers of a Brain Injury can be detected in the cerebrospinal fluid and in the blood directly after TBI

GFAP, glial fibrillary acid protein; MAP, microtubule-associated protein; MBP, myelin basic protein; NF, neurofilament; NSE, neuron-specific enolase; S100 astroglial calcium-binding protein; SBDP, spectrin breakdown products; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1

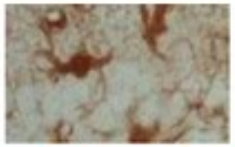
Adrian et al (2016). eNeuro 3. pii: ENEURO.0294-16.2016.



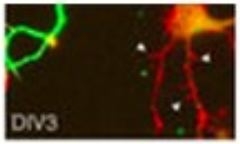
Cell body injury



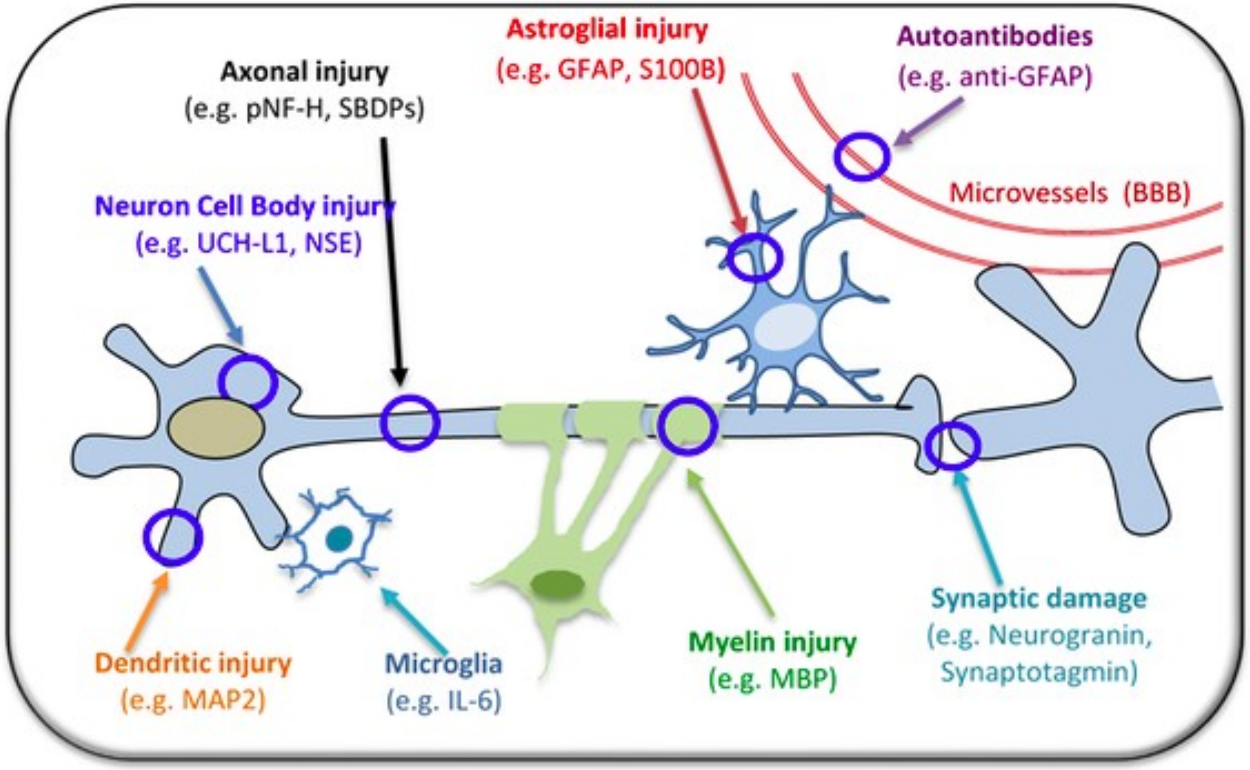
Gliosis/astroglia Injury



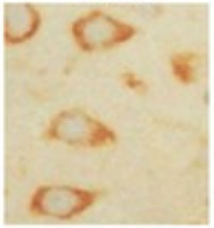
Astroglia/BBB damage



Tauopathy

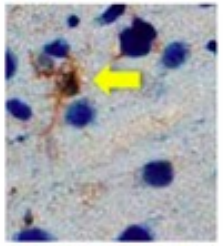


NSE



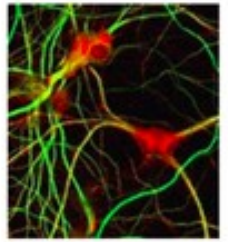
Cell body injury

Anti-GFAP AutoAb



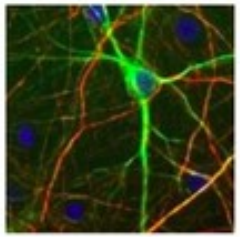
Autoimmunity

MAP2



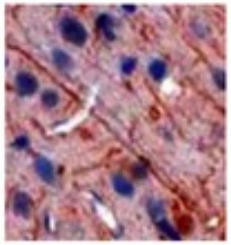
Dendritic injury

pNF-H



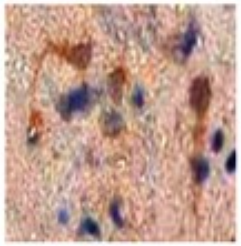
Axonal injury

SBDP150



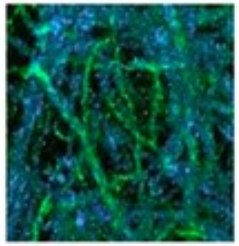
Necrosis

SBDP120



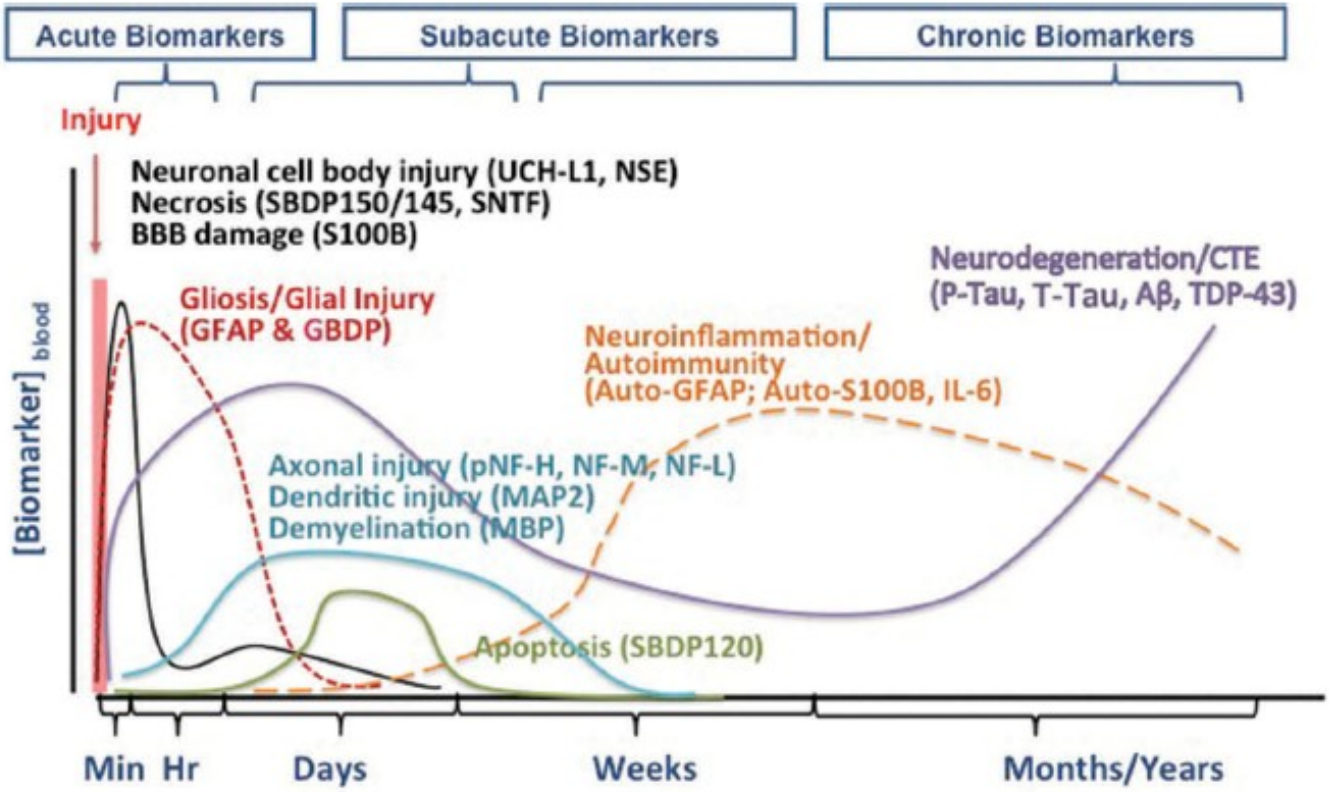
Apoptosis

MBP



Demyelination

Temporal Levels Following TBI



These biomarkers could represent different but parallel pathways active at various time points after the initial injury

CTE, chronic traumatic encephalopathy; GFAP, glial fibrillary acid protein; IL-6, interleukin-6; MAP, microtubule-associated protein; MBP, myelin basic protein; NF, neurofilament; NSE, neuron-specific enolase; S100B, astroglial calcium-binding protein; SBDP, spectrin breakdown products; SNTF, spectrin N-terminal fragment; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1

Wang et al (2018). Expert Rev Mol Diag 18:165–180.

Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting to Emergency Departments with Mild Brain Injury: A Living Systematic Review and Meta-Analysis

Table 1. Summary of the Number and Characteristics of Primary Articles Identified for Each Biomarker

Marker	*No. of studies*	*No. of participants*	*No. of studies (%) by no. of participants in each study*		*No. of studies by GCS*		*No. of studies with predefined cutoff*	*No of studies by sample type*	*Relevant results (Range individual sensitivities and specificities)*
S100B	22	7754 (CT+=713; CT-=7041)	50–100	4 (18)	GCS 15:	1	16	Serum 21	Sens 0.83–1.00
			101–200	7 (32)	GCS 14–15:	3		Plasma 1	Spec 0.12–0.77
			201–500	6 (27)	GCS 13–15:	15			
			>500	5 (23)	GCS 9–15:	2			
					GCS 3–15:	1			
GFAP	4	783 (CT+=198; CT-=595)	101–200	1 (25)	GCS 9–15:	3	0	Serum 3	Sens 0.67–1.00
			201–500	3 (75)	GCS 3–15:	1		Plasma 1	Spec 0.00–0.89
NSE	3	314 (CT+=55; CT-=259)	50–100	1 (33)	GCS 14–15:	1	0	Serum 3	Sens 0.56–1.00
			101–200	2 (67)	GCS 13–15:	2			Spec 0.07–0.77
UCH-L1	2	347 (CT+=64; CT-=283)	50–100	1 (50)	GCS 9–15:	2	0	Serum 2	Sens 1.00
			201–500	1 (50)					Spec 0.21–0.39
Tau	1	50 (CT+=10; CT-=40)	50–100	1 (100)	GCS 13–15:	1	0	Serum 1	Sens 0.50
									Spec 0.75

GCS, Glasgow Coma Scale; S100B, S100 calcium binding protein B; GFAP, glial fibrillary acidic protein; NSE, neuron specific enolase; UCH-L1, ubiquitin C-terminal hydrolase-L1.

S Mondello: *J Neurotrauma* 2021

Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting to Emergency Departments with Mild Brain Injury: A Living Systematic Review and Meta-Analysis

Results: S100B can help informed decision making in the ED, possibly reducing resource use; insufficient evidence that any of the other markers is ready for clinical application.

Serious are problems in the design, analysis, and reporting of many of the studies, and identified substantial heterogeneity and research gaps.

Conclusions: These findings emphasize the importance of methodologically rigorous studies focused on a biomarker's intended use, and defining standardized, validated, and reproducible approaches. The living nature of this systematic review, which will summarize key updated information as it becomes available, can inform and guide future implementation of biomarkers in the clinical arena.

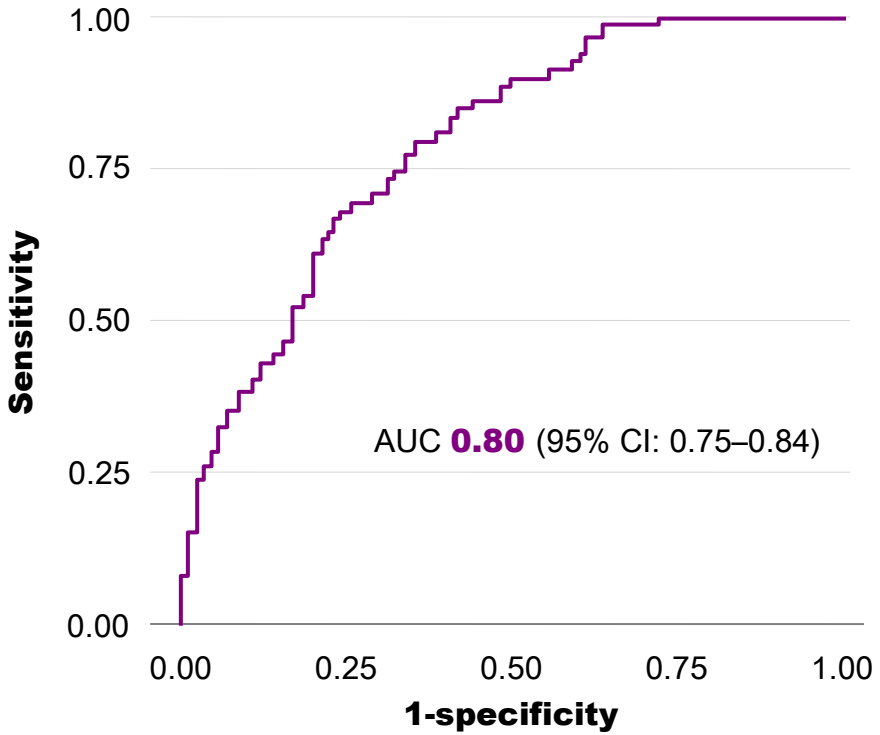
S Mondello: J NEUROTRAUMA 38:1086–1106, 2021

S100B is a Highly Sensitive Biomarker in mild TBI

- 1,309 patients with minor head injuries
- At a cutoff value of 0.10 µg/L, serum S100B identified patients with lesions on CT scan with a **sensitivity of 99%** and a specificity of 30%
- These values equate to a positive likelihood ratio (LR) of 1.4 and a negative LR of 0.03

Conclusion: An S100B concentration <0.10 µg/L reliably rules out the presence of cranial lesions in patients with mild head injury and could allow a **30% reduction in CT scans**

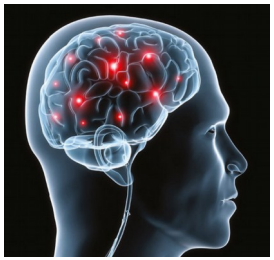
S100B sensitivity and specificity with respect to the radiological findings in the initial CT scan



CI, confidence interval; CT, computed tomography; ROC, receiver operating characteristic; S100B, astroglial calcium-binding protein; TBI, traumatic brain injury

Biberthaler et al (2006). Shock 25:446–453.

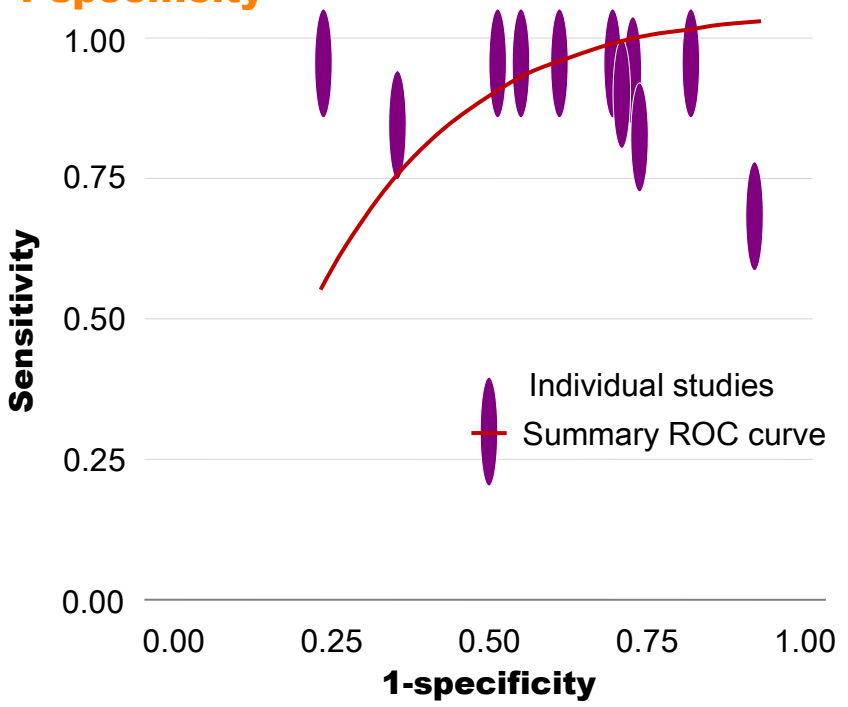
Low S100B levels predict Normal CT in mild TBI



- Meta-analysis of 12 clinical studies involving 2,466 pts with minor head injury
- Time from injury to S100B sampling: <3 Hrs to <24 hrs
- S100B had high sensitivity to predict a normal CT scan (pooled: 97%, range 75%–100%), very high NPVs (90%–100%)
- Where a cutoff of 0.10 µg/L could be evaluated, sensitivities and specificities were 96% and 30%, respectively

Conclusion: Low serum S100B levels accurately predict normal CT findings after minor head injury in adults

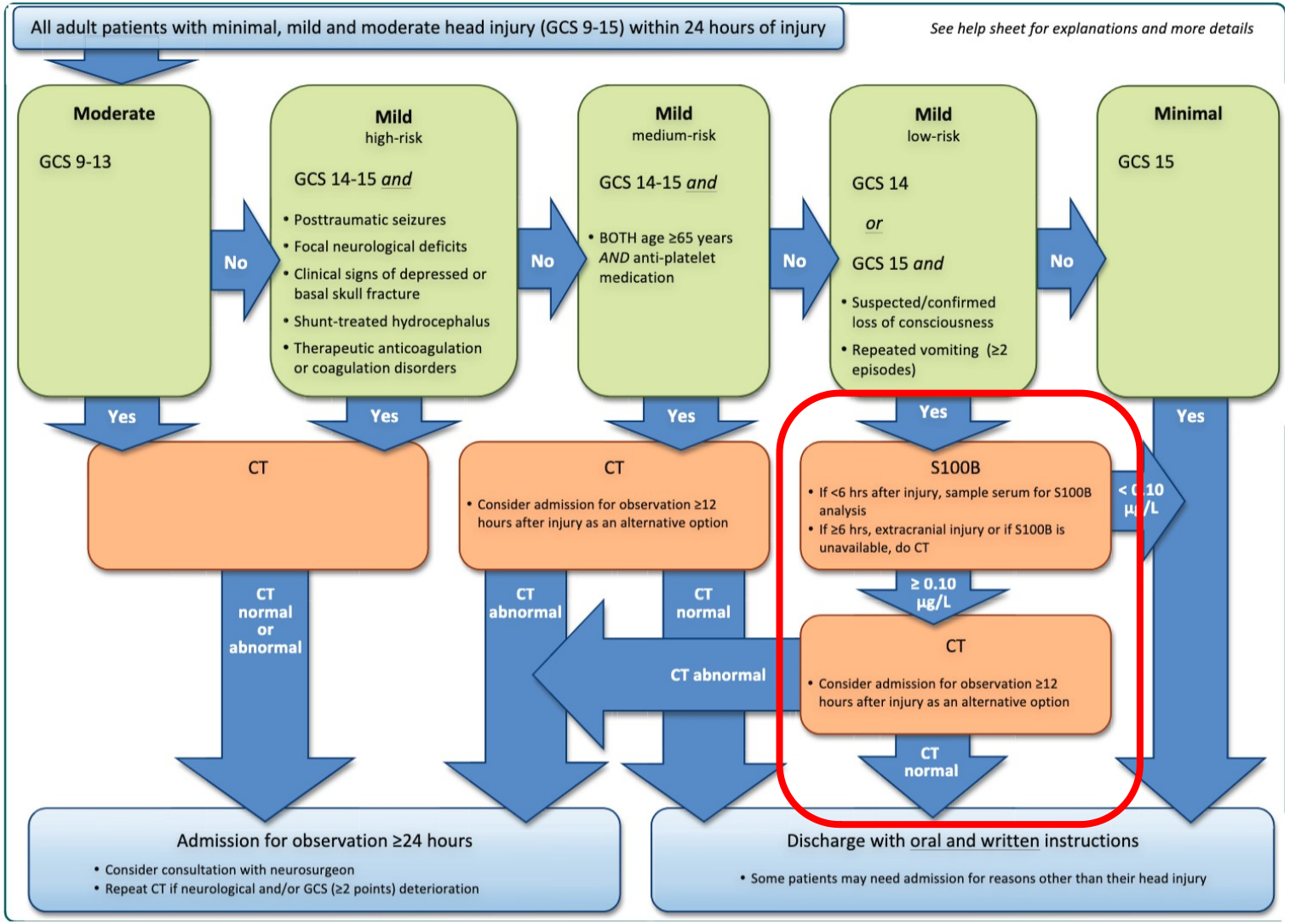
Summary ROC curve from all 12 studies showing the relationship of sensitivity vs. 1-specificity



CT, computed tomography; ROC, receiver operating characteristic; S100B, astroglial calcium-binding protein; TBI, traumatic brain injury **Undén et al (2010).** J Head Trauma Rehabil 25:228–240.

S-100B in adult pts. with low-risk mild head injury

Scandinavian Neurotrauma Committee recommendations



Undén et al (2013). BMC Medicine 11:50.

Scandinavian Guidelines incorporate the use of S100B to stratify pts for CT imaging.

Undén *et al. BMC Medicine* 2013, **11**:50
http://www.biomedcentral.com/1741-7015/11/50

BMC Medicine

GUIDELINE Open Access

Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update

Johan Undén[1*], Tor Ingebrigtsen[2] and Bertil Romner[3], for the Scandinavian Neurotrauma Committee (SNC)

"We recommend that adult patients after **mild head injury** with **GCS 14 and no risk factors** (anticoagulant therapy or coagulation disorders, post-traumatic seizures, clinical signs of depressed or basal skull fracture, focal neurological deficits), **or GCS 15 with loss of consciousness or repeated (≥2) vomiting and no other risk factors**, be sampled for analysis of S100B if **less than 6 h** have elapsed following trauma"

"If S100B measured within 6 hours of mild head injury is less than **0.10 µg/L**, the patient **may be discharged without a CT** (moderate quality, strong recommendation)"

CT, computed tomography; GCS, Glasgow Coma Scale; h, hours; S100B, astroglial calcium-binding protein
Undén et al (2013). BMC Medicine 11:50.

S100B-guided use of CT scans could reduce costs

- A cost analysis from the perspective of the Swedish health care system following the introduction of the Elecsys® S100B assay in 2007 showed that treatment costs* were:

n=726 adult patients with mild (GCS 14–15) TBI

Cost if S100B not used:

€281 per patient
(assumes CT scan used for 70% of patients, 52% of patients hospitalized for observation)

Actual costs incurred:

€242 per patient
(guideline compliance not perfect:
CT scan used for 55% of patients,
41% of patients hospitalized for observation)

€39 per patient saving

Cost if guidelines strictly followed:

(assumes CT scan only used for

patients with S100B >0.10 µg/L)

€71 per patient saving

The cost analysis did not include the opportunity costs related to time spent by patients in the ED and the socioeconomic costs associated with increased cancer risks from CT scans and therefore underestimates the cost-saving potential of S100B implementation

Treatment costs comprised S100B testing costs (€21 per test), CT scan costs (€130 per scan), and hospitalisation costs for observation for mild head injury (€366 per day)
CT, computed tomography; GCS, Glasgow coma score; S100B, astroglial calcium-binding protein; TBI, traumatic brain injury
Calcagnile et al (2016). BMC Neurol 16:200.

Prospective Validation of the Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries in Adults

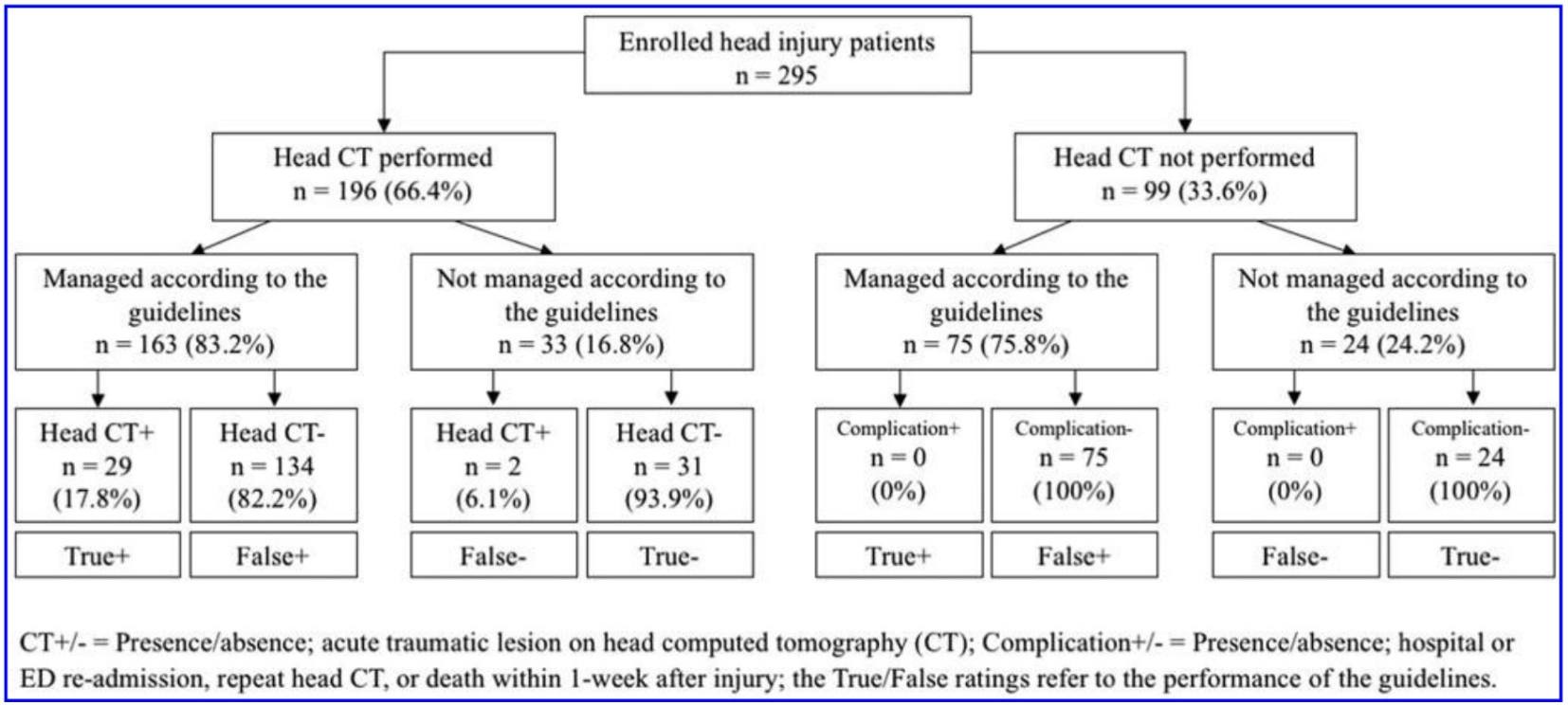


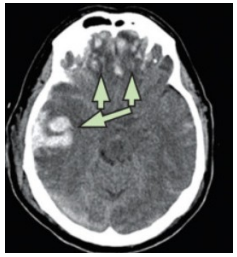
FIG. 2. Performance of the Scandinavian guidelines.

Mira Minkkinen, J Neurotrauma 2019

Heads Up to Clinicians:

Updated Mild Traumatic Brain Injury Guideline for Adults

A part of CDC's *"Heads Up"* Series



3. In patients with mild TBI, are brain-specific serum biomarkers predictive of an acute traumatic intracranial injury?

Level A recommendations: None specified.

Level B recommendations: None specified.

Level C recommendations: In mild TBI patients without significant extracranial injuries and a serum S-100B level < 0.1 µg/L measured within 4 hours of injury, consideration can be given to not performing a CT.**

**This test has not yet received Food and Drug Administration (FDA) approval for clinical use in the United States.

CDC SAFER·HEALTHIER·PEOPLE

American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

In Children US Guidelines recommend against Biomarker testing.

JAMA Pediatrics | Special Communication

Centers for Disease Control and Prevention Guideline on the Diagnosis and Management of Mild Traumatic Brain Injury Among Children

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- Recommendation 6: Health care professionals **should not use biomarkers outside of a research setting for the diagnosis of children with mild TBI**
- There is **insufficient evidence** to currently recommend any of the studied biomarkers for the diagnosis of mild TBI

  in children

Indicates there is still some way to go before S100B and other biomarkers are accepted

S100B, astroglial calcium-binding protein; TBI, traumatic brain injury

Lumba-Brown et al (2018). JAMA Pediatr 172:e182853.

Serum GFAP and UCH-L1 for Prediction of Absence of Intracranial Injuries on Head CT (ALERT-TBI): a Multicentre Observational study

1977 pts presenting to ED with a suspected, non-penetrating TBI GCS 9–15 at the time of informed consent.

The primary study outcomes were the sensitivity and the NPV of Glial fibrillary acidic protein (UCH-L1) and glial fibrillary acidic protein (GFAP) and the test result for the detection of traumatic intracranial injury on head CT.

	Sensitivity	Specificity	PPV	NPV	LRP	LRN
GCS 9–15 (n=1959)	0·976 (0·931–0·995)	0·364 (0·342–0·387)	0·095 (0·079–0·112)	0·996 (0·987–0·999)	1·5 (1·455–1·616)	0·07 (0·00–0·153)
GCS 14–15 (n=1920)	0·973 (0·924–0·994)	0·367 (0·345–0·390)	0·088 (0·073–0·105)	0·995 (0·987–0·999)	1·5 (1·457–1·618)	0·07 (0·00–0·159)
Neurosurgically manageable lesions (n=8)	1·00 (0·631–1·00)	0·344 (0·323–0·365)	0·006 (0·003–0·012)	1·00 (0·995–1·00)	1·5 (1·447–1·602)	0·0 (0·00–0·093)

)ata in parentheses are 95% CIs. PPV=positive predictive value. NPV=negative predictive value. LRP=likelihood ratio positive. LRN=likelihood ratio negative.

Table 3: **Performance of UCH-L1 and GFAP assay for predicting intracranial injury on head CT scan**

Interpretation: Pts with TBI who presented to European centres in the core study were older than were those in previous observational studies and often had comorbidities.

Most patients presented with mild TBI. The incomplete recovery of many patients should motivate precision medicine research and the identification of best practices to improve these outcomes.

Bazarian JJ, *Lancet Neurology 2019*

Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study

	Overall	ER stratum	Admission stratum	ICU stratum	p value*
(Continued from previous page)					
Biomarkers†					
NSE (ng/mlL; n=961)	18 (13–27)	13 (11–16·8)	14 (11–18)	23 (15–34)	<0·0001
S100B (µg/L; n=960)	0·18 (0·09–0·42)	0·07 (0·05–0·12)	0·11 (0·06–0·19)	0·30 (0·15–0·59)	<0·0001
GFAP (ng/mL; n=1010)	4·4 (0·8–17)	0·3 (0·1–1·0)	1·7 (0·6–5·1)	11 (3·4–31)	<0·0001
NFL (pg/mL; n=1010)	23 (10–60)	8·3 (5·1–15)	16 (8–30)	40 (18–95)	<0·0001
Total Tau (pg/mL; n=1010)	4 (1·7–11)	1·2 (0·8–2·0)	2·3 (1·3–4·5)	7·9 (3·3–17)	<0·0001
UCHL1 (pg/mL; n=1009)	127 (48–381)	35 (20–64)	68 (34–122)	275 (109–597)	<0·0001
Laboratory measurements					
Haemoglobin (g/dL; n=3846)	14 (12–15)	14 (13–15)	14 (13–15)	13 (12–14)	<0·0001
Glucose (mmol/L; n=3492)	6·9 (5·9–8·3)	6 (5·3–7·1)	6·5 (5·7–7·8)	7·3 (6·3–8·9)	<0·0001

Data are median (IQR) or n (%), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. TBI=traumatic brain injury. AIS=abbreviated injury score. ASA-PS=American Society of Anesthesiologists physical status classification system. GCS=Glasgow Coma Scale. S100B=S100 calcium-binding protein B. NSE=Neuron-specific enolase. NFL=neurofilament light. GFAP=glial fibrillary acidic protein. UCHL1=ubiquitin carboxy-terminal hydrolase L1. *p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata. †NSE and S-100B were measured using the e602 module of a Cobas 8000 analyser (Roche Diagnostics International, Rotkreuz, Switzerland) in Pécs, Hungary; and NFL, total tau, GFAP, and UCHL1 using the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, FL, USA.

Table 1: **Baseline characteristics of patients enrolled in the CENTER-TBI core study**

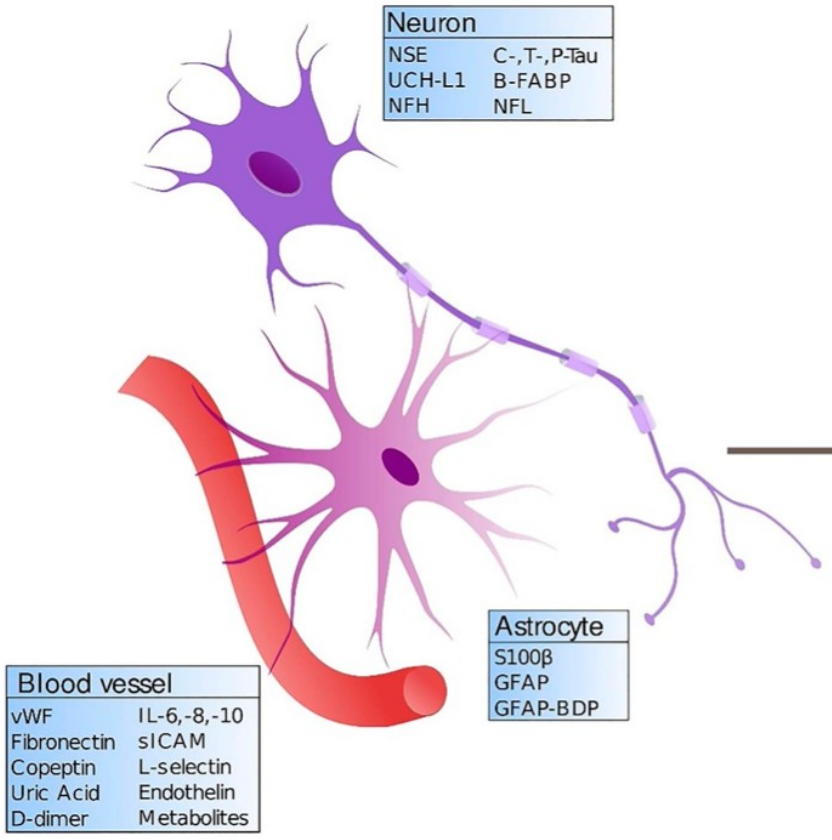
Steyerberg EW, *Lancet Neurology 2018*

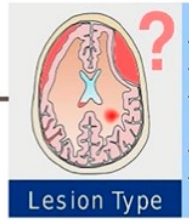
Blood Biomarkers and Structural Imaging Correlations Post-Traumatic Brain Injury: A Systematic Review

Biomarker	Number of studies	Total number of TBI cases per study (median [range])	Number of studies per age grouping	Number of studies per patient clinical severity GCS (mild—13-15, moderate—9-12, and severe—3-8)	Imaging modality used per study	Total percentage positive imaging (median [IQR])	Number o Scoring system/injury pattern
S100B	30	5276 (93 [9-1696])	Adult: 26 Pediatric: 3 Adult/ pediatric: 1	Not specified: 1 Mild: 7 Mild and moderate: 2 Mild, moderate, and severe: 13 Severe: 7	CT: 26 MRI: 1 CT and MRI: 3	68.67% (24.5, 99.85) Not specified: 6	Marshall: 13 Rotterdam: 4 Stockholm: 4 Self-created: 1 Diffuse vs Focal: 1
GFAP or GFAP-BDP	21	2825 (93 [9-450])	Adult: 19 Pediatric: 2	Not specified: 1 Mild: 4 Mild and moderate: 1 Mild, moderate, and severe: 9 Severe: 6	CT: 16 MRI: 2 CT and MRI: 3	72.8% (33.33, 98) Not specified: 4	Marshall: 11 Rotterdam: 2 Stockholm: 1 Self-created: 1
NSE	14	1494 (73 [13-417])	Adult: 12 Pediatric: 1 Adult/ pediatric 1	Not specified: 1 Mild, moderate, severe: 10 Severe: 3	CT: 13 CT, MRI: 1	99.8% (65.8,100) Not specified: 3	Marshall: 8 Rotterdam: 3 Stockholm: 3 Self-created: 1 Diffuse vs Focal: 1
Neurofilament proteins	9 (NF-H: 5 NF-L: 4)	756 (76 [9-182])	Adult: 8 Pediatric: 1	Mild: 2 Mild, moderate, and severe: 7	CT: 5 MRI: 3 CT and MRI: 1	72.6% (43.98, 96.95) Not specified: 3	Marshall: 5 Rotterdam: 2 Stockholm: 2
UCH-L1	8	1113 (114.5 [9-389])	Adult: 6 Pediatric: 1 Adult/ pediatric: 1	Mild: 2 Mild, moderate, and severe: 4 Severe: 2	CT: 7 CT and MRI: 1	72.8% (44.06,88) Not specified: 1	Marshall: 4 Rotterdam: 1 Stockholm: 1
Tau	7	633 (40 [34-196])	Adult: 6 Pediatric: 1	Mild, moderate, and severe: 5 Moderate and severe: 1 Severe: 1	CT: 6 MRI: 1	57.4% (44.9, 87.50) Not specified: 2	Marshall: 3 Rotterdam: 1 Stockholm: 1

Whitehouse, *Neurosurgery* 2022

Blood Biomarkers and Structural Imaging Correlations Post-Traumatic Brain Injury: A Systematic Review





- 28 papers
- NFH and tau may be raised in those with diffuse axonal injury[20,62,67]
- NSE and S100β may be higher in cerebral edema compared with other CT findings[22]
- Traumatic axonal injury may not be associated with a rise in GFAP[56]
- NFL is correlated to midline shift on MRI[12]

- 11 papers
- Overall positive correlation between biomarkers and lesion number and volume
- Positive correlations between S100β and contusion volume[25,48,50]
- Poor biomarker correlation with extra-axial hemorrhage[15]

- 30 papers
- Positive correlation between S100β, NSE, NFH, vWF, tau, and Marshall score[13,16,21,25,29,50,51,58,64]
- Inverse correlation between uric acid and Marshall score[23]
- Positive correlation between S100β, NSE, GFAP, UCH-L1, tau, and Rotterdam and Stockholm scores[12,58,59,61]
- Positive correlation between S100β, NSE, and Morris–Marshall score[39]

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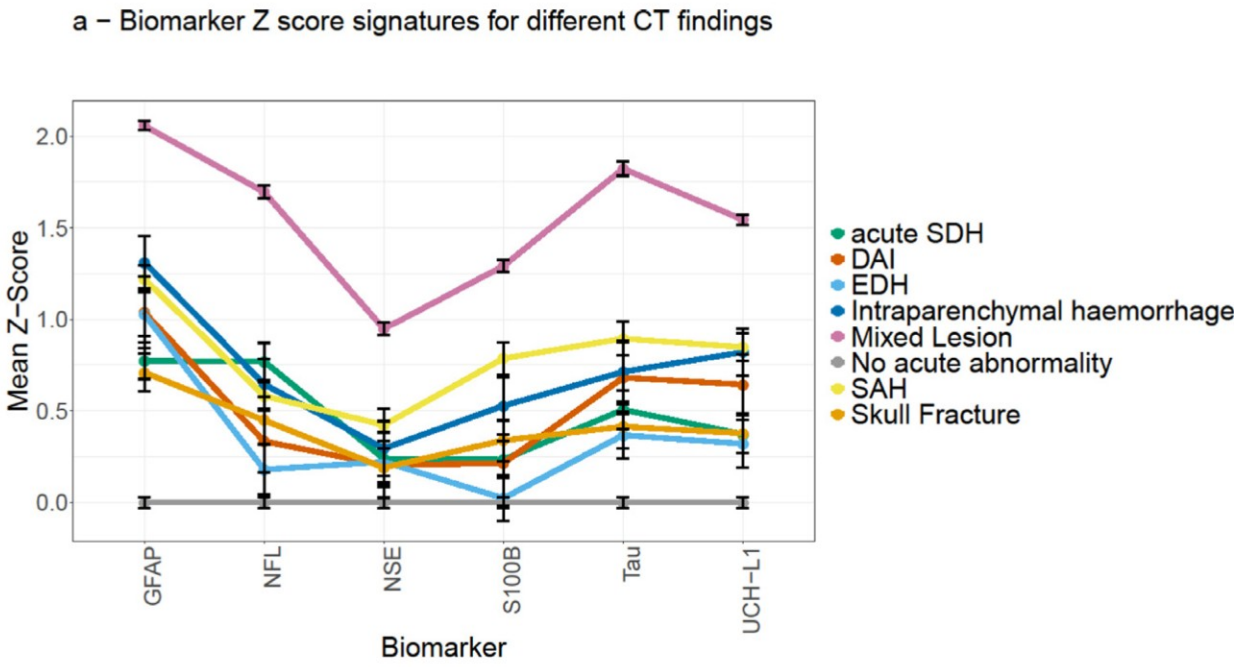
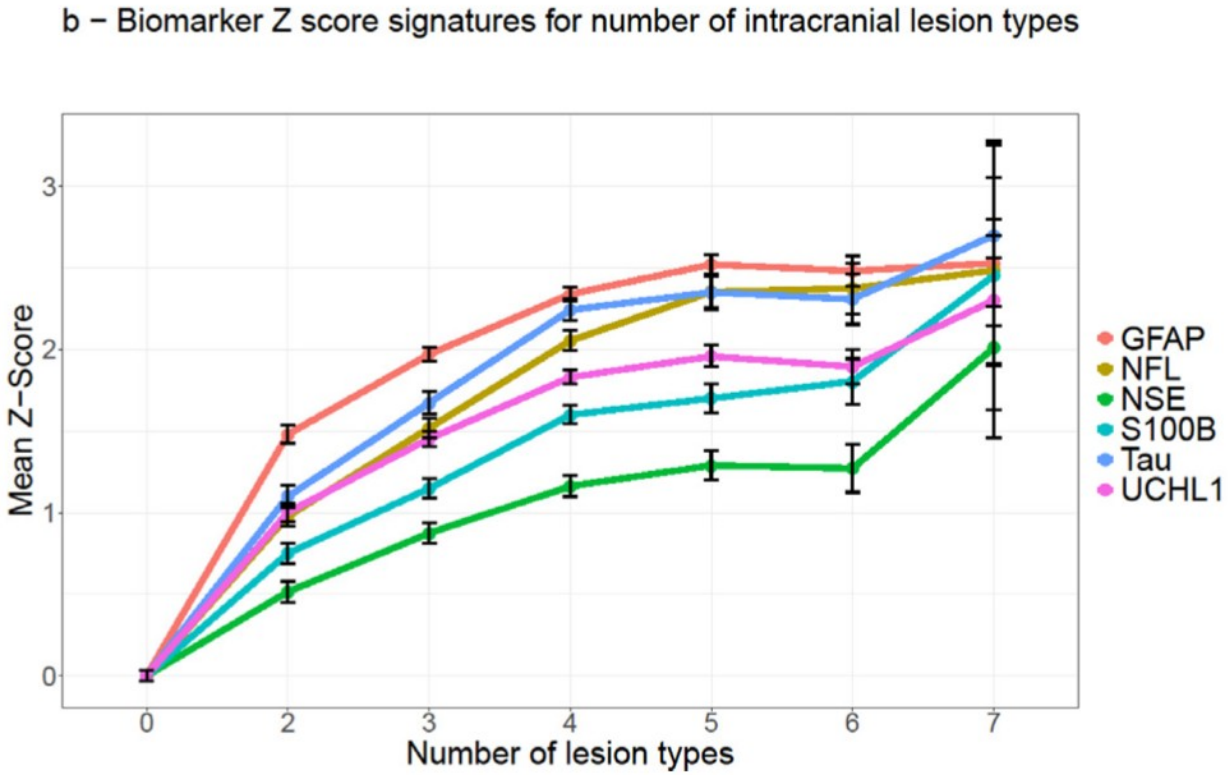
Relationship of Admission Blood Proteomic Biomarkers levels to Lesion type and Lesion burden in Traumatic Brain Injury: A CENTER-TBI study



Increased serum biomarkers (GFAP, NFL, NSE, S100B, t-tau and UCH-L1) measured in samples obtained <24 hours post-injury from 2869 pts with all severities of TBI, enrolled in the CENTER-TBI prospective cohort study.

Whitehouse The Lancet 2022

Relationship of Admission Blood Proteomic Biomarkers Levels to Lesion type and Lesion Burden in Traumatic Brain Injury: A CENTER-TBI study



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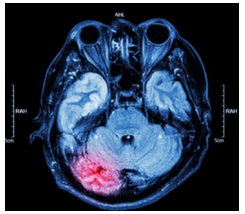
Conclusions



- Significant increase in interest in TBI biomarkers by the number of articles published
- Relationship between biomarkers levels and likelihood of Intracranial Injury

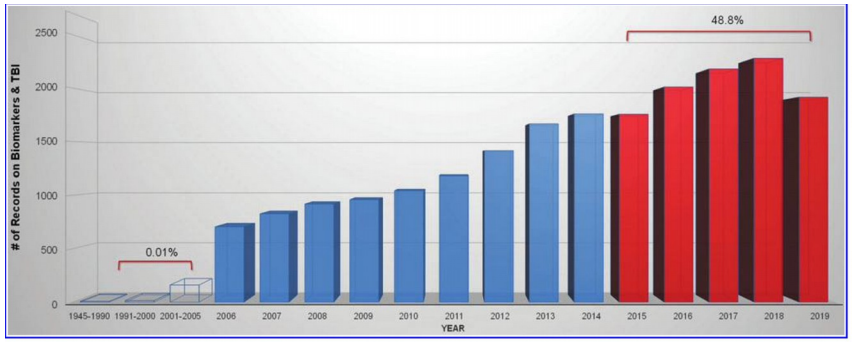


FIG. 2. The significant increase in interest in traumatic brain injury biomarkers as demonstrated by the number of articles published

- No relationship between biomarkers and type of intracranial Injury
- Evidences (research studies) for high NPV for intracranial injury in subjects with low biomarker levels (low-cut off sensivity levels).
- Undefined application in current practice ….

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