Biomarcatori nel Trauma Cranico Lieve: Aggiornamenti e Prospettive

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TBI: more than one definition

Definitions of TBI vary considerably[1–6] resulting in difficulties in diagnosis and case ascertainment

According to the CDC[5]: "Traumatic brain injury (TBI) is caused by a bump, blow, or jolt to the head that disrupts the normal function of the brain"

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

World Health Organization

1. Wang et al (2018). Expert Rev Mol Diag 18:165–180; 2. Maas et al (2017). Lancet Neurol 16:987–1048;
3. Carroll et al (2004). J Rehabil Med 43(Suppl):113–125; 4. Kay et al (1993). J Head Trauma Rehabil 8:86–87;
5. Centers for Disease Control and Prevention (CDC). Traumatic Brain Injury & Concussion. Available at: https://www.cdc.gov/traumaticbraininjury/index.html. Accessed November 2018;
6. Menon et al (2010). Arch Phys Med Rehabil 91:1637–1640.

TBI ranges from mild to severe

Classification of TBI severity

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness	0–30 min	> 30 min and < 24 hrs	> 24 hrs
Alteration of consciousness / mental state	a moment up to 24 hrs	> 24 hrs Severity based on other criteria	
Post-traumatic amnesia	0-1 day	> 1 and < 7 days	> 7 days
Glasgow Coma Scale (best available score in first 24 hrs)	13–15	9–12	< 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.

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.

*Stein S, **Ann Emerg Med** 2009*

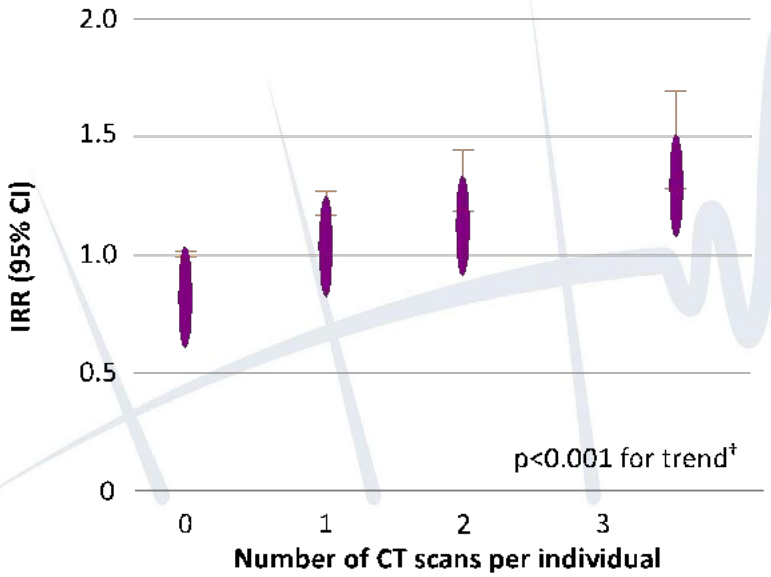
CT scans rate: Canadian CT head rule (high risk only) 53%, Canadian 56%, the Neurotraumatology Committee of the World Federation of Neurosurgical Societies 56%, New Orleans 69%, NEXUS-II 56%, National Institute of Clinical Excellence 71%, and the Scandinavian 50%.

Sensitivity for any intracranial lesion ranged from 95.7% (95% CI 93% to 97%) (Scandinavian) to 100% (95%CI 98% to 100%) (National Institute of Clinical Excellence). Specificities varied between 30.9% (95% CI 30% to 32%) (National Institute of Clinical Excellence) and 52.9% (95% CI 52% to 54) (Scandinavian).

Conclusion: NEXUS-II and the Scandinavian clinical decision aids displayed the best combination of SE and SP. Therefore, choosing which of the 2 clinical decision instruments to use must be based on decisionmakers' attitudes toward risk.

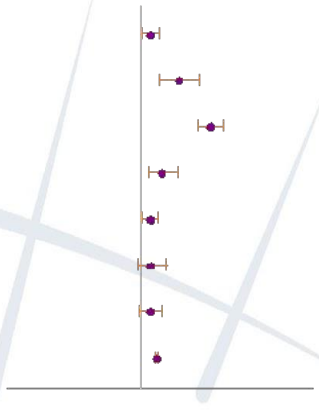
Ionizing radiation increases cancer risk

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.

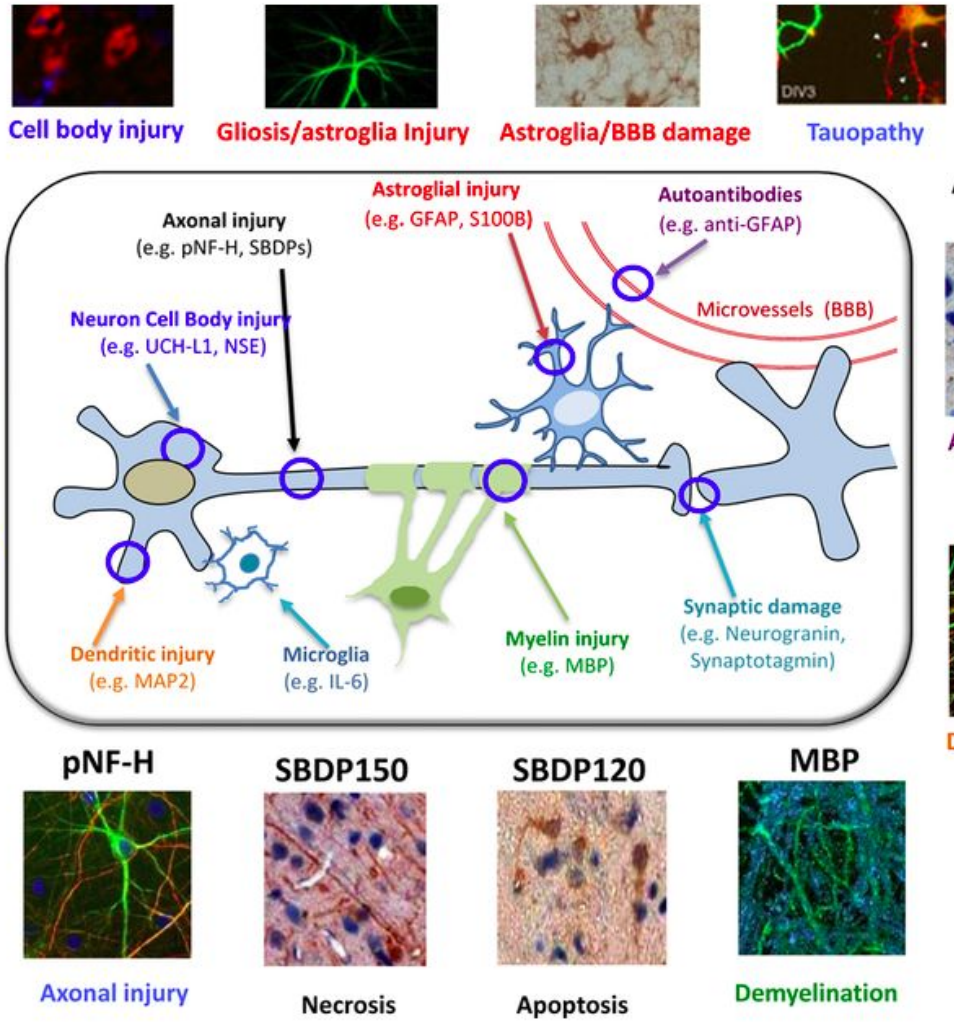
† Overall cancer incidence was 24% greater for exposed vs unexposed (IRR 1.24; 95% CI 1.20–1.29). The IRR increased by 0.16 for each additional scan.

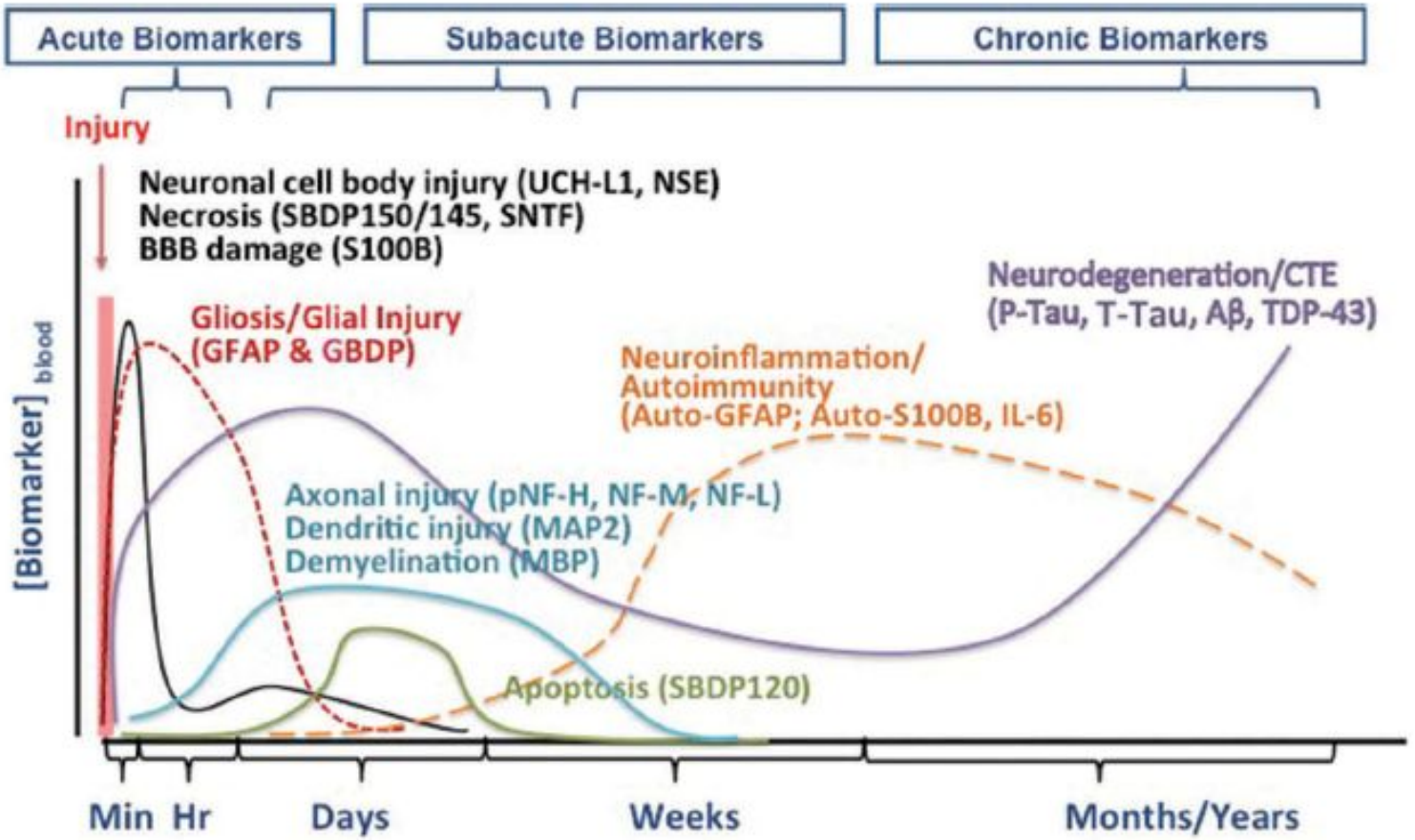
Mathews et al (2013). BMJ 346:f2360.

TBI biomarkers to better understand the disease mechanism

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.


Cell body injury
Gliosis/astroglia Injury
Astroglia/BBB damage
Tauopathy
DIV3
Anti-GFAP AutoAb
Autoimmunity
Astroglial injury
(e.g. GFAP, S100B)
Autoantibodies
(e.g. anti-GFAP)
Axonal injury
(e.g. pNF-H, SBDPs)
Microvessels (BBB)
Neuron Cell Body injury
(e.g. UCH-L1, NSE)
NSE
Cell body injury
MAP2
Dendritic injury
Synaptic damage
(e.g. Neurogranin, Synaptotagmin)
Myelin injury
(e.g. MBP)
Dendritic injury
(e.g. MAP2)
Microglia
(e.g. IL-6)
pNF-H
SBDP150
SBDP120
MBP
Axonal injury
Necrosis
Apoptosis
Demyelination



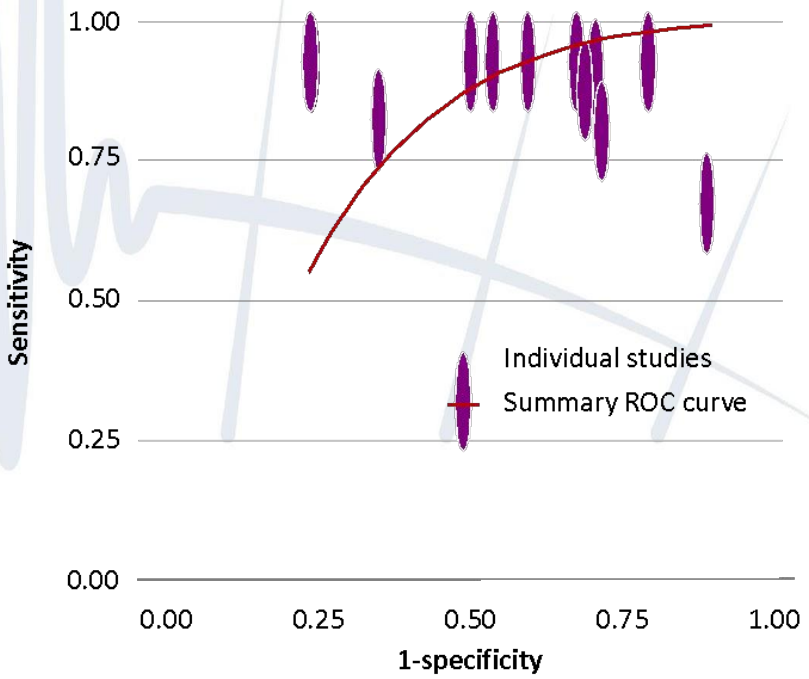
CTE, chronic traumatic encephalopathy; GFAP, glial fibrillary acid protein; IL-6, interleukin-6; MAP, microtubule-associated protein; MBP, myelin basic protein; NF, neurofilament; NSE, neuron-specific enolase; S100B, astroglial calcium-binding protein; SBDP, spectrin breakdown products; SNTF, spectrin 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.

Low serum S100B levels accurately predict normal CT findings 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

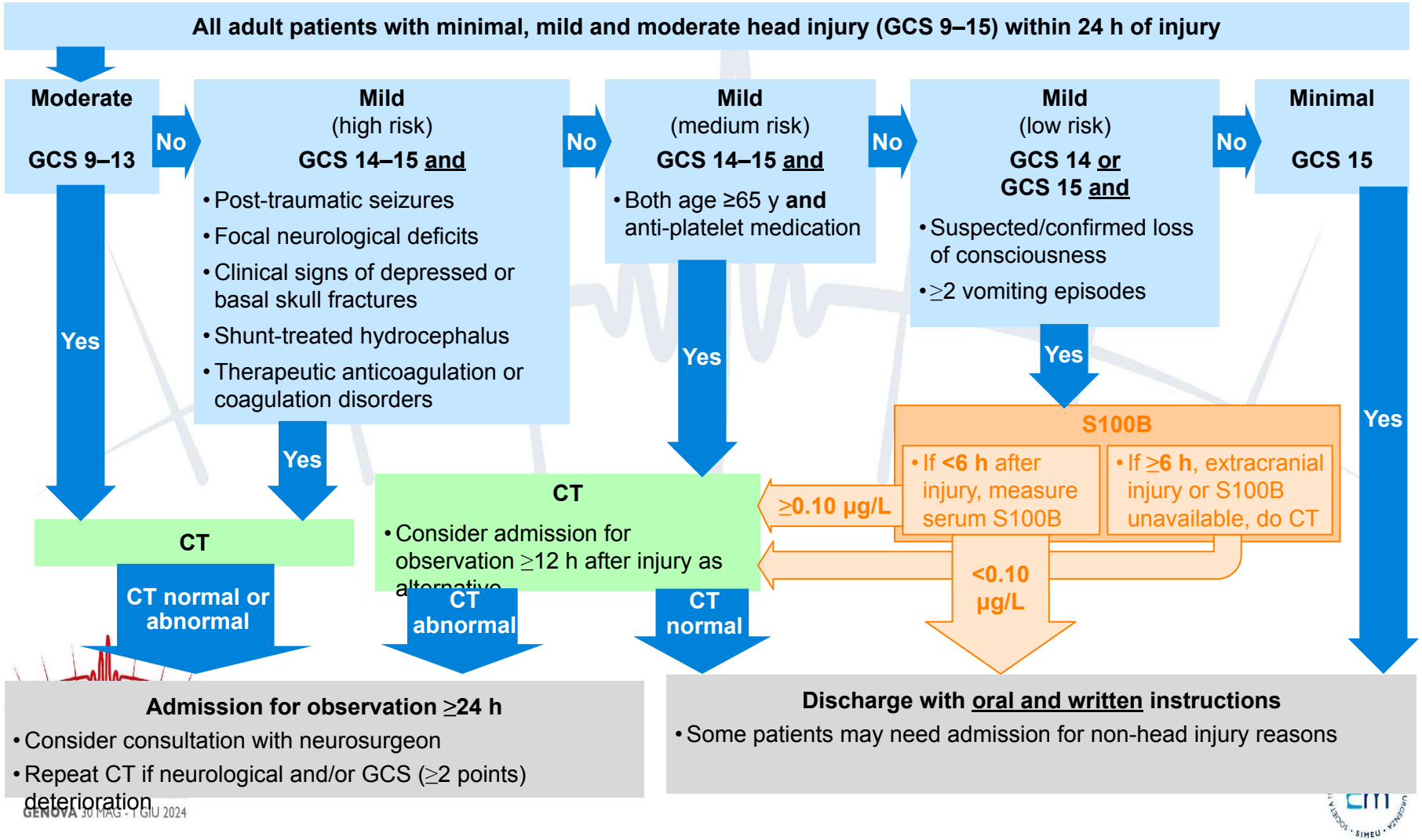
Summary ROC curve from all 12 studies showing the relationship of sensitivity vs. 1-specificity



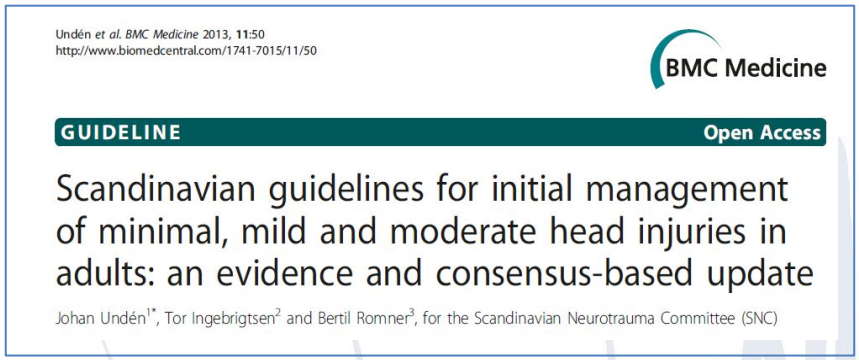
Conclusion: Low serum **S100B levels accurately predict normal CT findings** after minor head injury in adults

S-100 in adult pts. with low-risk MHI

Scandinavian Neurotrauma Committee recommendations



Scandinavian guidelines incorporate the use of S100B to stratify patients 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 hrs 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.

Level C recommendation by ACEP for the use of S100B in mild TBI

American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

TRAUMA/CLINICAL POLICY

Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting

"Level C recommendation

In mild TBI patients without significant extracranial injuries and a **serum S-100B level less than 0.1 µg/L** measured within 4 hrs of injury, consideration can be given to **not performing a CT**."

Level C recommendation for the use of S100B. However, the test has no Food and Drug Administration approval for clinical use in the United States to date.

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

Jagoda et al. (2008) Ann Emerg Med 52:714-748

GFAP plus UCH-L1 rule out the need for CT scan in adults with TBI with high sensitivity

The multicentre, observational ALERT-TBI[1] study (1977 adults with TBI; GCS 9–15) investigated the combination of:

GFAP (cutoff 22 pg/mL)

UCH-L1 (cutoff 327 pg/mL)

For detection of intracranial injury, the combination test had:

Sensitivity: **97.6%** (95% CI: 93.1–99.5%)

NPV: **99.6%** (95% CI: 98.7–99.9%)

GFAP and UCH-L1 are FDA approved for evaluation of adult patients with suspected mild TBI (GCS 13–15) when used within 12 hours of suspected head injury along with other clinical information[2]

CI, confidence interval; GCS, Glasgow coma score; GFAP, glial fibrillary acidic protein; NPV, negative predictive value; TBI, traumatic brain injury; UCH-L1, ubiquitin C-terminal hydrolase-L1

1. Bazarian et al (2018). Lancet Neurol 17:782–789; 2. Banyan BTITM package insert. Available at www.banyanbio.com/banyan-bti.html

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (**ALERT-TBI**): a multicentre observational study

Neurotrauma Reports
Mary Ann Liebert, Inc. publishers

	Sensitivity	Specificity	PPV	NPV
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)
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)
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)

Data 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

High SE and NPV of the **UCH-L1 a**nd **GFAP** test. This supports its potential clinical role for ruling out the need for a CT scan among patients with TBI presenting at ED in whom a head CT is felt to be clinically indicated.

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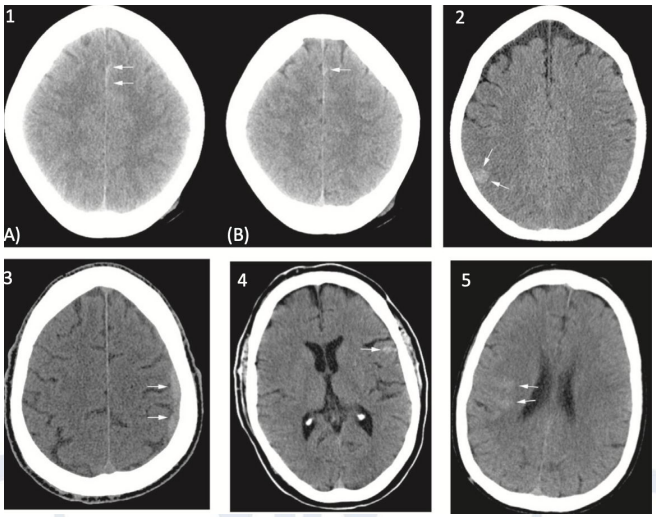
Bazarian: **Lancet Neurol**. 2018 Sep;17(9):782-789

Head CT images of false-negative subjects.



Sex	Age (years)	Time from injury (h)	GCS	GFAP (pg/ml)	UCH-L1 (pg/ml)	Head CT findings[b]
Male	62	8.9	15	16	84	Acute SDH
Female	49	5.9	15	24[a]	94	SAH
Female	43	3.5	15	19	58	Parenchymal hematoma
Male	41	3.3	15	26[a]	82	SAH
Male	44	2.9	13	28[a]	184	SAH

Bazarian: Acad Emerg Med. 2021;28:1308–1317.

Neuroinflammatory Biomarkers for Traumatic Brain Injury Diagnosis and Prognosis: A TRACK-TBI Pilot Study

Neurotrauma Reports
Mary Ann Liebert, Inc. publishers

Table 2. Markers Discriminating TBI Clinical Diagnosis and Severity

Clinical diagnosis: TBI vs. HC

Biomarker	*AUC*	*TBI*	*HC*	*Sig. (p)*
IL-6	0.924 [0.880–0.967]	1.47 [0.55–4.07] pg/mL	0.15 [0.10–0.22] pg/mL	<0.001
IL-10	0.863 [0.804–0.922]	0.17 [0.10–0.39] pg/mL	0.05 [0.04–0.08] pg/mL	<0.001
HMGB-1	0.860 [0.802–0.919]	47.48 [24.35–146.79] ng/mL	20.77 [14.88–20.77] ng/mL	<0.001
IL-4	0.819 [0.731–0.907]	0.09 [0.07–0.15] pg/mL	0.06 [0.06–0.07] pg/mL	<0.001
IL-7	0.764 [0.637–0.891]	0.61 [0.25–1.29] pg/mL	2.32 [0.90–3.67] pg/mL	<0.001
IL-8	0.764 [0.666–0.862]	3.46 [1.53–12.58] pg/mL	1.29 [0.50–1.64] pg/mL	0.001
TARC	0.749 [0.626–0.872]	16.23 [10.49–29.74] pg/mL	40.63 [22.08–56.31] pg/mL	<0.001
IL-5	0.748 [0.621–0.874]	0.37 [0.26–0.49] pg/mL	0.24 [0.16–0.35] pg/mL	<0.001
IL-16	0.727 [0.642–0.813]	146.17 [107.02–309.52] pg/mL	110.04 [98.74–114.16] pg/mL	0.002

Yue et al.; Neurotrauma Reports 2023, 4.1

Question: What is the role of biomarkers in the evaluation and management of pts admitted to an ED for mTBI?

R2.2.1 - The experts suggest to use blood-based assay of protein S100B, when it is available, during the 3 hrs following mild TBI, in pts at intermediate risk, the objective being to limit the number of brain scans.

EXPERT OPINION (STRONG AGREEMENT)

R2.2.2 - The experts suggest to use blood-based assay combining UCH-L1 and GFAP, when they are available, during the 12 hrs following mild TBI, in pts at intermediate risk, the objective being to limit the number of brain scans.

EXPERT OPINION (STRONG AGREEMENT)

C. Gil-Jardine´, J.-F. Anaesth Crit Care Pain Med (2023)

Argumentation

Amoo et al., (meta-analysis) serum GFA with a threshold of 22 pg/mL detects TBI by CT scan with a SE 93% [73–99], SP 36% [12–68].

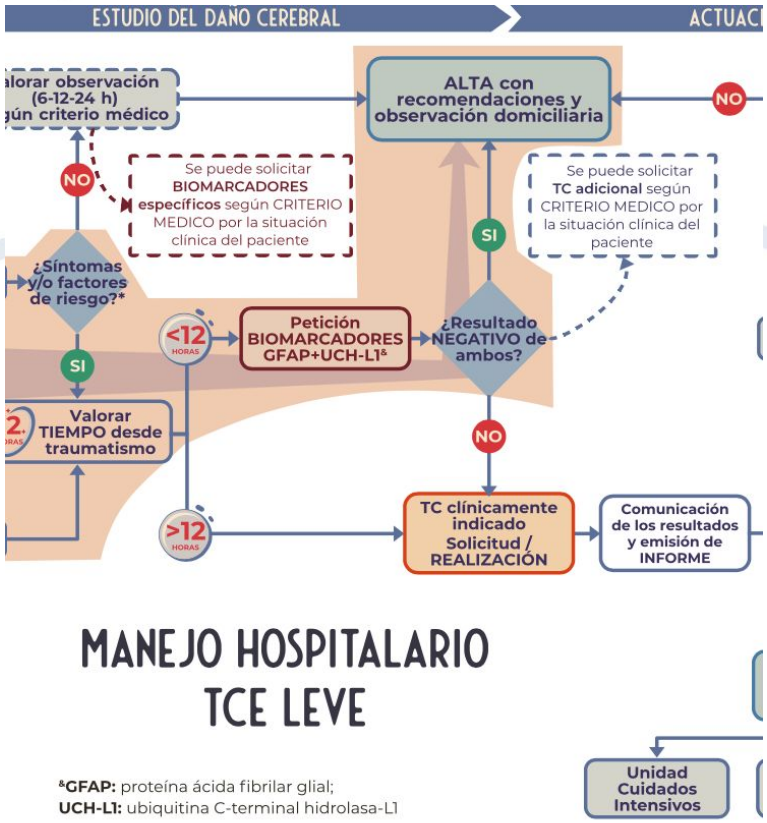
Rogan et al., (meta-analysis: 6 studies)) the diagnostic accuracy of serum GFAP in detecting intracranial lesions; SE 67% to 100% and SP 0% to 89%, while the NPV of GFAP ranged from 72.1% to 100%. For serum UCH-L1, (4 studies) SE 61% – 100%, and SP 21% – 63.7% with NPV to rule out a lesion by CT scan 70.7% to 100%.

A combination of UCH-L1 and GFAP serum (1 study) <12 hrs from trauma, at thresholds of 327 pg/mL and 22 pg/mL, **rules out an intracranial lesion** (SP 36.7% [34.5–39.0], SE 97.3% [92.4–99.4], NPV 99.5% [98.7– 99.9]).

C. Gil-Jardine´, J.-F. Anaesth Crit Care Pain Med (2023)

Traumatismo craneoencefálico leve y biomarcadores de lesión cerebral aguda

Francisco Temboury Ruiz[1], Francisco Moya Torrecilla[2], Miguel Ángel Arráez Sánchez[3], Ignacio Arribas Gómez[4], Agustina Vicente Bártulos[5], Francisco José Gallego España[6], Miriam Menacho Román[7], Audrey Morales Rodríguez[8], Daniel Morell-García[9], Inés Pecharromán de las Heras[10], José Roberto Penedo Alonso[11], José Antonio Prieto Arruñada[12], Fernando Rosell Ortiz[13], Carlos Sánchez Rodríguez[14]



Temboury Ruiz F, et al. Rev Esp Urg Emerg. 2024;3:31-36

Take home

- Il test diagnostico di riferimento resta la diagnostica per immagini (TC cranio encefalo).
- Le LG attuali si basano su elementi clinici ad un TC rate 50-70%, accuratezza 90-92% (falsi negativi 0.3% ???).
- I marcatori nei casi a basso rischio (asintomatici) potrebbero aggiungere elementi decisionali, anche se mancano dati solidi.
- I marcatori potrebbero migliorare l'appropriatezza degli esami TC, (riduzione di costi e radio-esposizione per quel 90% dei casi negativi).
- La qualità degli studi e il grado delle raccomandazione ad oggi sono ancora di basso grado.