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Blood biomarkers to identify patients with different intracranial lesion combinations after traumatic brain injury

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ABSTRACT

Introduction: There is a lack of studies examining the most promising blood biomarkers for traumatic brain injury (TBI) in relation to gross pathology types.
Research question: To examine whether the admission levels of blood biomarkers can discriminate patients with different combinations of traumatic intracranial findings from patients with negative computed tomography (CT) scans.

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Material and methods: One hundred thirty patients with all severities of TBI were studied. Seventy-five had CT-positive and 55 CT-negative findings. CT-positive patients were divided into three clusters (CL) using the Helsinki CT score: focal lesions (CL1), mixed lesions (CL2) and mixed lesions + intraventricular haemorrhage (CL3). CT scans were obtained upon admission and blood samples taken within 24 h from admission. S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), heart fatty-acid binding protein (H-FABP), neurofilament light (NF-L), interleukin-10 (IL-10), total-tau (t-tau), and β-amyloids 1–40 (Aβ40) and 1–42 (Aβ42) were analysed from plasma samples. CT-negative cluster was used as control.
Results: GFAP, Aβ40 and Aβ42 levels differed between the clusters, but not significantly. NF-L and t-tau discriminated CL1 from CT-negative cluster with AUCs of 0.737 and 0.771, respectively. NF-L, t-tau and GFAP discriminated CL2 from CT-negative cluster with AUCs of 0.839, 0.781 and 0.840, respectively. All biomarkers analysed were able to discriminate CL3 and CT-negative cluster.
Discussion and conclusion: All studied biomarkers distinguished the most severely injured cluster, CL3, from CT-negative cluster. The results may reflect the severity of TBI but also show that biomarkers have a variable ability to identify patients with combinations of intracranial traumatic lesions in the examined time window.

Abbreviations

Aβ40	β-amyloid 1-40
Aβ42	β-amyloid 1-42
ASDH	acute subdural haematoma
AUC	area under the curve
AUC-ROC	Area Under the Receiver Operating Characteristic curve
CL	cluster
CL1	cluster 1
CL2	cluster 2
CL3	cluster 3
CT	computed tomography
CT-	CT-negative patients
CT+	CT-positive patients
ED	emergency department
EDH	epidural haematoma
FDA	the Food and Drug Administration
GFAP	glial fibrillary acidic protein
GOSE	Glasgow outcome scale extended
HCTS	Helsinki CT score
FDR	false discovery rate
H-FABP	heart fatty-acid binding protein
IL-10	interleukin-10
tICH	traumatic intracerebral haematoma
ISS	injury severity score
IQR	interquartile range
IVH	intraventricular haemorrhage
LLoD	lower limit of detection
LLoQ	lower limit of quantification
moTBI	moderate TBI
mTBI	mild TBI
NF-L	neurofilament light
S100B	S100 calcium-binding protein B
SD	standard deviation
SDH	subdural haematoma
sTBI	severe TBI
TBI	traumatic brain injury
tSAH	traumatic subarachnoid haemorrhage
t-tau	total-tau

1. Introduction

Traumatic brain injury (TBI) is a complex injury involving numerous cellular structures and cell compartments (Maas et al., 2008). Macroscopic structural lesions (Vande et al., 2020; Richter et al., 2022) often occur in different combinations and distributions. These include focal and diffuse, haemorrhagic and non-haemorrhagic lesions (Vande et al., 2020). Several biomarkers expressed in different parts of brain cells have been examined in the acute diagnostics of TBI. Despite decades of TBI biomarker research, there is a lack of studies examining the most promising blood biomarkers for TBI in relation to intracranial gross pathology types of the injury. This information would be highly important in bringing the TBI biomarkers widely into clinical practice.

S100 calcium-binding protein B (S100B), primarily expressed in astrocytes (Anderson et al., 2001), is the most widely studied biomarker in TBI research. The Scandinavian Guideline recommends discharging patients with mild TBI (mTBI) without risk factors from the emergency department (ED) without a CT scan if S100B level is below 0.10 μg/l less than 6 h from the injury (Undén et al., 2013). Glial fibrillary acidic protein (GFAP) is the main structural protein filament in the astroglial cytoskeleton (Petzold et al., 2004), and its use in a combination assay together with ubiquitin C-terminal hydrolase L1 has been approved by the Food and Drug Administration (FDA) (Bazarian et al., 2018). Axonal proteins (Johnson and Stoothoff, 2004; Binder et al., 1985) neurofilament light (NF-L) (Zanier et al., 2011) and tau have been found to detect CT abnormalities in patients with acute TBI (Rubenstein et al., 2017; Posti et al., 2019). Persistently elevated NF-L levels with moderate (moTBI) or sTBI have been associated with worse outcome (Tuure et al., 2024; Newcombe et al., 2022). Heart-type fatty acid binding protein (H-FABP) is expressed in the neuronal cytoplasm (Wunderlich et al., 2005) and may be able to discriminate CT-positive from CT-negative patients with mTBI especially in combination with GFAP and IL-10 (Lagerstedt et al., 2017). β-Amyloid isoforms 1–40 (Aβ40) and 1–42 (Aβ42) are formed from the β-amyloid precursor protein by proteolysis (Haass et al., 2012). Aβ40 and Aβ42 are less studied as acute phase biomarkers in TBI. TBI also elicits inflammatory responses with various pro- and anti-inflammatory cytokines (Rodney et al., 2018). Interleukin-10 (IL-10) has neuroprotective properties (Garcia et al., 2017) and is helpful in differentiating CT-negative patients with mTBI from the CT-positive ones (Lagerstedt et al., 2018).

The main aim of this study was to investigate whether blood levels of TBI-related protein biomarkers (S100B, GFAP, H-FABP, NF-L, t-tau, Aβ40, Aβ42 and IL-10) from diverse cellular origin can differentiate various lesion types and their combinations on head CT scans. Correlations with functional outcome were assessed to add clinical relevance of the findings. The hypothesis of the study is based on both quantitative and qualitative differences in biomarker profiles related to the type and extent of TBI. In terms of quantitative differences of TBI-associated blood biomarker levels, the hypothesis is that deeper brain injuries, often associated with larger volumes of injured tissue, e.g. in traumatic

intracerebral haematoma (tICH) and intraventricular haematoma (IVH), probably lead to greater release of biomarkers into bloodstream. Regarding qualitative differences, we hypothesised that biomarkers are more specific to certain types of brain injury allowing us to conduct an exploratory study of the response of biomarkers in the blood to different lesion combinations.

2. Materials and methods

2.1. Study population

Patients with all severities of TBI were recruited for a prospective study at Turku University Hospital between November 2011 and October 2013 from 8 a.m. to 10 p.m. (convenience sampling). The population consisted of patients with isolated TBI and TBI with extracranial injuries. The study was part of the EU-funded TBIcare project (Evidence-based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries, Grant Agreement 270259). The study was approved by Southwest Finland Hospital District Research Ethics Committee (decision 68/180/2011).

The inclusion criteria for the study were age ≥18 years with clinical diagnosis of TBI and indications for acute head CT according to National Institute for Health and Care Excellence criteria (Eades, 2014). Exclusion criteria were suspected TBI without an indication for CT, elapsed time from the injury > two weeks, blast-induced or penetrating injuries, prior major neurological disease, inability to live independently, chronic subdural haematoma, inability to speak Finnish, or no consent obtained. Patients or their proxies were given oral and written study information and written consent was obtained.

2.2. TBI severity assessment

The severity of the TBI was assessed using the Glasgow Coma Scale (GCS). The lowest GCS score before possible intubation was used. GCS 13–15 was classified as mTBI; GCS 9–12 moTBI, and GCS 3–8 as sTBI.

2.3. ISS score

Total injury severity score (ISS), extracranial and cranial separately, were calculated to determine the severity of the extracranial injuries. Extracranial ISS ≥4 was considered major injury.

2.4. Head computed tomography classifications

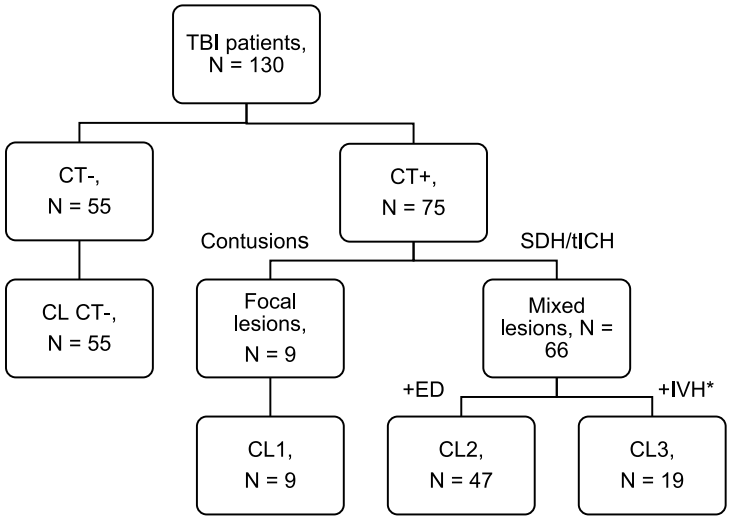
Admission CT scans were classified according to Helsinki CT score (HCTS) (Raj et al., 2014) by three senior neurotrauma clinicians/researchers (JPP, RR, TML). JPP and RR independently and blindly analysed the scans, TML assessed the results. Conflicting results were solved in group discussions.

2.5. Clusters

CT-positive patients were divided into three clusters based on lesion types on head CT according to HCTS, validated outcome predictor of TBI (Fig. 1). (Raj et al., 2014) CL1 consisted of patients with focal lesions <25 cm^3 in volume, normal suprasellar cisterns and contusions. CL2 and CL3 included patients with mixed lesions over 25 cm^3 in size, subdural haematomas (SDH) and/or tICH. All patients with epidural haematoma (EDH) were included in CL2. Patients with IVH and mixed lesions (SDH and/or tICH) were included in the most severely injured group CL3, except for two patients who also had EDH and thus were included in CL2. The patients with a CT-negative TBI served as a reference cluster.

2.6. Biomarker analyses

A blood sample for biomarker analysis was obtained within 24 h from hospital admission. Due to a few late referrals the samples were not always collected within 24 h from the injury. The elapsed time from injury to blood sampling is presented as median and interquartile range (IQR). The blood samples were centrifuged for 10 min at 10,000 rpm at 4 °C, and plasma was immediately frozen and stored at −70 °C for analysis. NF-L, GFAP and t-tau levels were measured using the Human Neurology 4-Plex A assay (N4PA) on an HD-1 Single molecule array (Simoa) instrument from Quanterix (Quanterix, Billerica, MA). LLoD (lower limit of detection) for NF-L, GFAP, and t-tau was 0.104 pg/ml, 0.221 pg/ml, and 0.024 pg/ml, respectively. LLoQ (lower limit of quantification) for these biomarkers was 0.241 pg/ml, 0.467 pg/ml, and 0.053 pg/ml. Calibration for NF-L ranged from 0.533 pg/ml to 453 pg/ml, and for GFAP and t-tau the ranges were from 0.987 pg/ml to 725 pg/ml, and 0.136 pg/ml to 112 pg/ml, respectively. The K151HTD kit was



The Helsinki Computerized Tomography Score

Mass lesion type(s)	
- Subdural haematoma	2 points
- Intracerebral haematoma	2 points
- Epidural haematoma	-3 points
Mass lesion size > 25 cm^3	2 points
Intraventricular haemorrhage	3 points
Suprasellar cisterns	
- Normal	0 points
- Compressed	1 point
- Obliterated	5 points
Sum score	-3 to 14 points

Fig. 1. Clustering of the patients with TBI according to the Helsinki CT score.
*Two patients with both EDH and IVH were included in CL2.
CL1 = cluster 1, CL2 = cluster 2, CL3 = cluster 3, CL CT- = CT-negative cluster, CT = computed tomography, CT- = CT-negative patients, CT+ = CT-positive patients, EDH = epidural haematoma, tICH = intracerebral haematoma, IVH = intraventricular haemorrhage, SDH = subdural haematoma, TBI = traumatic brain injury.
CL1: Focal contusions; CL2: Mixed lesions (SDH and tICH) and all EDH's; CL3: Mixed lesions (SDH and tICH), all patients had IVH, none had EDH; CT-neg: CT negative cluster.

used to analyze H-FABP and K151QUD for IL-10, both from Meso Scale Diagnostics (Meso Scale Diagnostics, Rockville, MD, USA). LLoD for H-FABP was 0.103 ng/ml with a calibration range of 0.137–100 ng/ml. LLoQ had not been established as the test has not been fully validated yet. LLoD for IL-10 was 0.04 pg/ml with LLoQ being 0.298 pg/ml, and the calibration rate being 0.0774–317 pg/ml. S100B was measured using EZHS100B-33K kit from Millipore (Millipore, Billerica, MA, USA). LLoD was 2.7 pg/ml, with calibration ranging from 2.7 to 2000 pg/mL. A duplex Simoa immunoassay by Quanterix (Billerica, MA, USA) was used to analyze the levels of Aβ40 and Aβ42. The LLoD was 0.045 pg/ml and 0.142 pg/ml, and the LLoQ 0.142 pg/ml and 0.69 pg/ml for Aβ40 and Aβ42, respectively. The calibration for Aβ40 and Aβ42 ranged from 0 pg/ml to 90.0 pg/ml, and from 0 pg/ml to 11.0 pg/ml, respectively. No samples were below the LLoDs and LLoQs. All the kits were used according to the manufacturers' recommendations. The measurements were performed by board-certified laboratory technicians blinded to clinical data using one batch of reagents in one round of experiments. Intra-assay coefficients of variation monitored using high and low QC samples that were common across plates, were below 10% for all analytes.

2.7. Glasgow outcome scale extended

Glasgow outcome scale extended (GOSE) was evaluated between six and sixteen months by an experienced neurologist (OT). GOSE assesses a patient's functional outcome from an injury ranging from deceased to full recovery (Wilson et al., 1998, 2021).

2.8. Statistical analysis

We used all accessible data without estimating the sample size beforehand. Data were analysed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC). Continuous variables that followed a normal distribution were summarized with mean and standard deviation (SD) and other continuous variables with median (IQR). Categorical variables were characterized using frequencies and percentages. Difference between the continuous background variables/demographic variables and clusters were tested using one-way ANOVA or non-parametric Kruskal-Wallis test. In case of categorical variables Chi-Squared test or Fisher's exact test was used. The Kolmogorov-Smirnov test was used to assess the normality of the biomarkers. The Kruskal-Wallis test was used to compare the biomarker levels between the clusters. False discovery rate (FDR) correction for multiple testing was used for p-values. An adjusted P-value <0.05 was considered statistically significant. Biomarker correlations with the HCTS, GOSE and age were analysed with Spearman correlation. The ability of the biomarkers to differentiate the clusters from CT-negative patients was analysed using AUROC curves. An AUC of 0.8–1.0 was considered good, AUC of 0.7–0.8 adequate, and AUC <0.7 poor (Safari et al., 2016).

2.9. Data analysis statement

De-identified data not published in the article can be shared by request with a qualified investigator.

3. Results

Out of the 200 recruited patients, 130 had all the biomarkers and a head CT scan. 75 (58%) patients were CT-positive and 55 (42%) were CT-negative. Demographics of patients are presented in Tables 1 and 2. For those patients whose exact time of injury was known (n = 56, 43%), the median (IQR) time elapse from injury to blood sampling was 11 h

Table 1
Demographics of the study cohorts.

Variable type	Variable	CL1, n = 9	CL2, n = 47	CL3, n = 19	CT-neg, n = 55	p
Demographic	Age (years, mean ± SD)	48.33 ± 22.71	53.49 ± 19.47	45.42 ± 20.75	43.67 ± 18.21	0.082
	Sex (male/female), n (%)	7 (78)/2 (22)	39 (83)/8 (17)	15 (79)/4 (21)	34 (62)/21 (38)	0.0971
	GCS [median (IQR)]	15 (13–15)	14 (9–15)	9 (4–11)	15 (14–15)	**<0.0001**
	mTBI, n (%)	7 (77.8)	29 (61.7)	3 (15.8)	51 (92.7)	
	moTBI, n (%)	0 (0.0)	7 (14.9)	7 (36.8)	3 (5.5)	
	sTBI, n (%)	2 (22.2)	11 (23.4)	9 (47.4)	1 (1.8)	
	ISS [median (IQR)]					
	total	6 (4–22)	16 (9–25)	25 (9–27)	3 (1–9)	**<0.0001**
	cranial	4 (4–16)	9 (4–16)	16 (9–25)	1 (1–4)	**<0.0001**
	extracranial	2 (0–16)	0 (0–8)	2 (0–9)	0 (0–8)	0.811
	Pat. with extracranial injury, n (%)	3 (33)	18 (38)	7 (37)	19 (35)	
	Pupil reactivity, n (%)					
	Unreactive/reactive	0 (0)/9 (100)	4 (10)/36 (90)	5 (29)/12 (71)	1 (2)/53 (98)	**0.0065**
	Outcome, n (%)					
	Favourable (GOSE 5–8)	7 (78)	27 (57)	9 (47)	51 (93)	**<0.0001***
	Unfavourable (GOSE 1–4)	2 (22)	20 (43)	10 (53)	4 (7)	
	Complete (GOSE 8)	1 (11)	7 (15)	0 (0)	23 (42)	**0.0002′**
	Incomplete (GOSE 1–7)	8 (89)	40 (85)	19 (100)	32 (58)	
HCTS	Mass lesion types, n (%)					
	Subdural haematoma	0 (0)	43 (91)	10 (53)	0 (0)	**<0.0001**
	Traumatic intracerebral haematoma	9 (100)	30 (64)	14 (74)	0 (0)	**<0.0001**
	Epidural haematoma	0 (0)	11 (23)	0 (0)	0 (0)	**<0.0001**
	Mass lesion size >25 cm^3, n (%)	0 (0)	20 (43)	6 (32)	0 (0)	**<0.0001**
	Intraventricular haemorrhage, n (%)	0 (0)	2 (4)	19 (100)	0 (0)	**<0.0001**
	Suprasellar cisterns, n (%)					
	Normal	9 (100)	21 (45)	10 (53)	55 (100)	
	Compressed	0 (0)	23 (49)	8 (42)	0 (0)	**<0.0001**
	Obliterated	0 (0)	3 (6)	1 (5)	0 (0)	0.201
	Sum [median (IQR)]	2 (2–2)	4 (2–5)	6 (5–8)	0 (0)	**<0.0001**

EDH = epidural haematoma, GCS = Glasgow coma scale, GOSE = Glasgow outcome scale - extended, HCTS = Helsinki CT score, tICH = traumatic intracerebral haematoma, ISS = injury severity score, IVH = intraventricular haemorrhage, Pat. = patients, SD = standard deviation, SDH = subdural haematoma, TBI = traumatic brain injury.
CL1: Focal contusions; CL2: Mixed lesions (SDH and tICH) and all EDH's; CL3: Mixed lesions (SDH and tICH), all patients had IVH, none had EDH; CT-neg: CT negative cluster.
P-value <0.05 was considered statistically significant (bolded). *GOSE 1–4 vs GOSE 5–8. 'GOSE 1–7 vs 8.

Table 2
Comparison of the patient clusters.

Variable type	Variable	p-value CL1 vs CL2	p-value CL1 vs CL3	p-value CL2 vs CL3	p-value CL1 vs CT-neg	p-value CL2 vs CT-neg	p-value CL3 vs CT-neg
Demographic	GCS	0.270	**0.030**	**0.018**	0.265	**<0.0001**	**<0.0001**
	ISS						
	total	0.262	0.088	0.124	0.134	**<0.0001**	**<0.0001**
	cranial	0.095	**0.016**	0.123	**0.003**	**<0.0001**	**<0.0001**
HCTS	Sum	**0.0031**	**<0.0001**	**0.0013**			

GCS = Glasgow coma scale, HCTS = Helsinki CT score, ISS = injury severity score.
ISS total: the injury severity score of the patient including all the injuries (brain and external injuries); ISS cranial: the injury severity score due to the brain injury.
CL1: Focal contusions; CL2: Mixed lesions (SDH and tICH) and all EDH's; CL3: Mixed lesions (SDH and tICH), all patients had IVH, none had EDH; CT-neg: CT negative cluster.
P-value <0.05 was considered statistically significant (bolded).

(4–18.5). The exact injury time was unavailable for 74 patients, of which 28 were sampled within 24 h and 46 after 24 h of the injury.

73% (n = 95) of the patients were male. After dividing the patients into clusters, CL1, CL2 and CL3 contained 9, 47 and 19 patients, respectively. The total ISS score was lowest in CT-negative and highest in CL3 with median (IQR) of 3 (1–9) and 25 (9–27) ($p < 0.0001$), respectively. 47 (36%) patients had major extracranial injury, 33–38% in each cluster. The most severely injured patients were in CL3, mainly consisting of patients with moTBI or sTBI, n = 16 (84%). Most patients in CT-negative cluster were mTBI, n = 51 (92%) and had favourable outcomes (GOSE 5–8), n = 51 (93%). GOSE was assessed within 6–9 months for 105 (81%) patients, the rest between 10 and 16 months.

The biomarker levels between the three CT-positive clusters were compared (Table 3). The levels of GFAP, Aβ40 and Aβ42 differed between CL1, CL2 and CL3, p = 0.047, 0.036 and 0.048 respectively.

Table 4 and Figs. 2–4 demonstrate the ability of the biomarkers to distinguish CL1, CL2, and CL3 from the CT-negative patients. NF-L and t-tau were able to distinguish CL1 from the CT-negative patients with AUCs of 0.737 and 0.771, respectively. NF-L, t-tau and GFAP distinguished CL2 from the CT-negative patients with AUCs of 0.839, 0.781 and 0.840, respectively. All studied biomarkers were able to distinguish the most severely injured patient group, CL3, from the CT-negative patients with NF-L and GFAP having the highest AUCs of 0.936 and

Table 4
The ability of the biomarkers to distinguish between ct-negative and ct-positive clusters, auc-roc comparisons.

Biomarker origin	Biomarker	AUC[a]	AUC[b]	AUC[c]
astroglial	S100B	0.479	0.583	**0.720**
	GFAP	0.638	**0.840**	**0.912**
neuronal	H-FABP	0.683	0.617	**0.708**
axonal	NF-L	**0.737**	**0.839**	**0.936**
	t-tau	**0.771**	**0.781**	**0.849**
	Aβ40	0.543	0.661	**0.728**
	Aβ42	0.613	0.575	**0.750**
inflammatory	IL-10	0.661	0.690	**0.784**

AUCs >0.7 are highlighted.
CL1: Focal contusions; CL2: Mixed lesions (SDH and tICH) and all EDH's; CL3: Mixed lesions (SDH and tICH), all patients had IVH, none had EDH; CT-neg: CT negative cluster.
EDH = epidural haematoma, tICH = traumatic intracerebral haematoma, IVH = intraventricular haemorrhage, SDH = subdural haematoma.
[a] CT-negative patients vs CL1.
[b] CT-negative patients vs CL2.
[c] CT-negative patients vs CL3.

Table 3
Biomarker levels by clusters.

	Biomarker		CL1 median (IQR)	CL2 median (IQR)	CL3 median (IQR)	CT-neg median (IQR)	p -value[a] 1 vs 2 vs 3	p-value[b] 1 vs 2	p-value[c] 1 vs 3	p-value[d] 2 vs 3
Astroglial	S100B	pg/ml	90.3 (63.2–164)	102 (55.1–237)	215 (60.4–381)	85.9 (56.9–135)	0.155	0.616	0.116	0.318
	GFAP	ng/ml	1.46 (0.27–13.7)	11.5 (1.95–43.9)	39.1 (6.91–99.5)	0.51 (0.14–1.64)	**0.047**	0.501	0.116	0.318
Neuronal	H-FABP	ng/ml	8.10 (5.58–36.1)	6.75 (4.76–21.7)	11.1 (5.50–43.2)	5.48 (2.99–13.2)	0.414	0.616	0.712	0.343
Axonal	NF-L	pg/ml	51.9 (12.4–70.1)	66.2 (19.8–179)	67.5 (41.7–117.6)	11.2 (6.67–16.2)	0.440	0.616	0.252	0.695
	t-tau	pg/ml	8.65 (4.0–21.6)	13.8 (2.54–41.6)	29.2 (4.21–55.7)	2.11 (1.18–3.08)	0.426	0.616	0.252	0.442
	Aβ40	pg/ml	17.1 (11.0–21.5)	24.5 (15.6–31.4)	27.4 (17.3–37.4)	17.0 (12.4–20.8)	**0.036**	0.391	0.111	0.343
	Aβ42	pg/ml	10.3 (6.56–21.4)	19.5 (11.5–27.1)	21.9 (18.1–32.2)	16.5 (12.5–19.2)	**0.048**	0.461	0.111	0.318
inflammatory	IL-10	pg/ml	0.68 (0.42–1.59)	0.95 (0.42–2.49)	1.79 (0.77–3.46)	0.40 (0.23–1.22)	0.213	0.746	0.252	0.318

Statistically significant values ($p < 0.05$) are highlighted.
CL1: Focal contusions; CL2: Mixed lesions (SDH and tICH) and all EDH's; CL3: Mixed lesions (SDH and tICH), all patients had IVH, none had EDH, CT-neg: CT negative cluster.
EDH = epidural haematoma, FDR = false discovery rate, tICH = traumatic intracerebral haematoma, IVH = intraventricular haemorrhage, SDH = subdural haematoma.
[a] Comparison: CL1 vs CL2 vs CL3, Kruskal-Wallis test.
[b] Comparison: CL1 vs CL2, Kruskal-Wallis test, p-value with FDR correction.
[c] Comparison: CL1 vs CL3, Kruskal-Wallis test, p-value with FDR correction.
[d] Comparison: CL2 vs CL3, Kruskal-Wallis test, p-value with FDR correction.

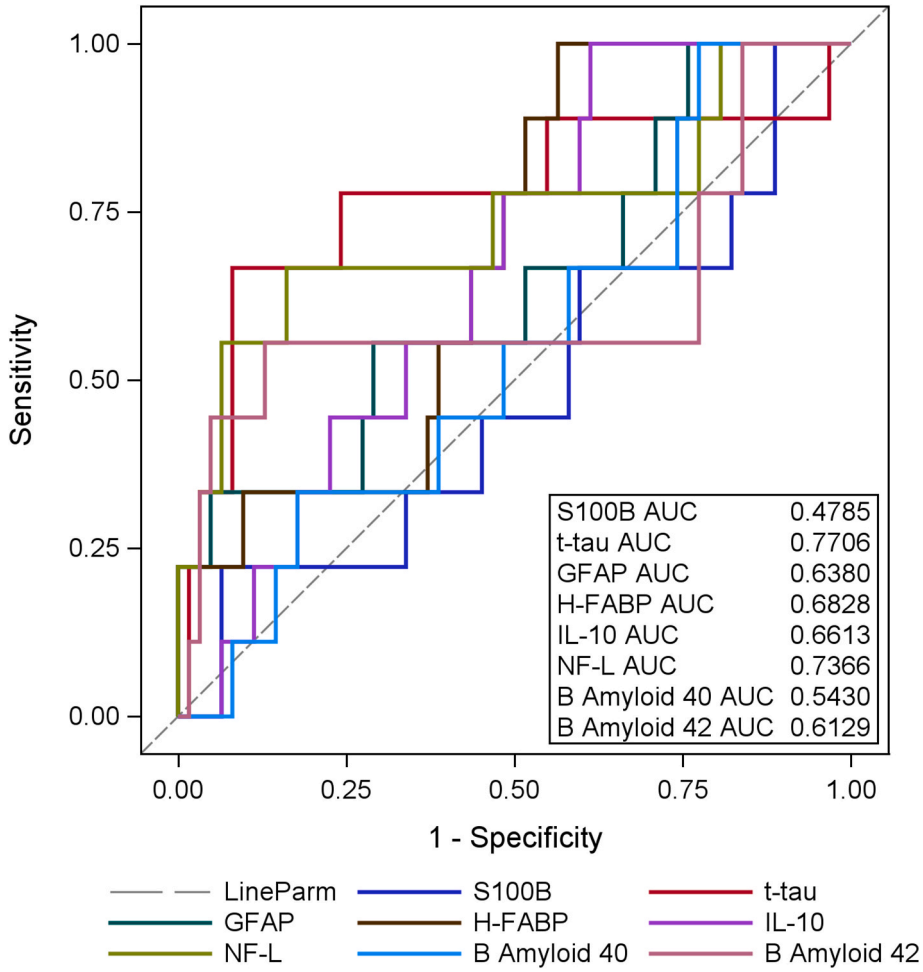


Fig. 2. The ability of the biomarkers to distinguish between ct-negative and the ct-positive cluster CL1, auc-roc curves.

0.912, respectively.

Correlations of different biomarkers, the HCTS sum, age and GOSE were compared between the CT-positive clusters (Table 5). The HCTS sum had a significant positive correlation with the levels of GFAP, NF-L, t-tau, IL-10, Aβ40, and S100B, and a negative correlation with GOSE. The HCTS sum had mild correlation with age and the levels of H-FABP and Aβ42. Age had a significant negative correlation with GOSE and a positive with NF-L.

4. Discussion

In this prospective, observational single-center study, the blood protein biomarkers of patients with all severities of TBIs were analysed and their levels were compared with the head CTs on admission. Only NF-L and t-tau could distinguish CT-positive from CT-negative patients, regardless of whether they have focal or mixed intracranial lesions. All analysed biomarkers adequately discriminated between the CT-negative patients and the most severely injured cluster of patients, CL3 (IVH and mixed lesions). Correlations with functional outcome were assessed to add clinical relevance of the findings where the sum of HCTS and age were found to have a significant negative correlation with GOSE.

Intracranial injuries are known to increase several different biomarker levels, but the dynamic pathophysiology is still poorly understood. Admission biomarker studies to date have mainly focused on CT-positive patients without focusing on the type or combinations of traumatic abnormalities. Only few studies examining different biomarkers in specific lesion types have been conducted (Whitehouse et al., 2022; Undén et al., 2005; Wolf et al., 2015).

A CENTER-TBI study by Whitehouse et al. examined serum biomarkers in different CT findings evaluated with Marshall CT score (Whitehouse et al., 2022). They found that the extent and number of the lesions was more important than the lesion type with the highest biomarker levels associated with large intraparenchymal haemorrhage, oedema or IVH. Diagnostics by lesion type was unsuccessful as many patients had several kinds of lesions and the corresponding number of patients with only one type of lesion was small (Whitehouse et al., 2022).

Our study differs from the above study (Whitehouse et al., 2022). In our study, the patients were divided into three groups based on the outcome-weighted HCTS (Raj et al., 2014) and the clinical diagnostic value of the biomarkers in different lesion combinations was assessed. The HCTS sum had a significant positive correlation with all other biomarkers except for Aβ42 and H-FABP and a negative correlation with GOSE.

SDH, tICH, traumatic subarachnoid haemorrhage (tSAH), and IVH have been associated with unfavourable prognosis (Maas et al., 2007), whereas EDH has more favourable outcome (Maas et al., 2007). tSAH is not an independent predictor in HTCS and is not included in the classification (Raj et al., 2014). The study patients with mixed lesions were divided into groups based on the existence of EDH or IVH as most of those patients also had SDH, tICH or both. Whitehouse et al. concluded that the biomarker levels could not be used as specific lesion markers but rather reflected the severity of the injury (Whitehouse et al., 2022). This is in line with our findings as all the studied biomarkers distinguished CL3 with AUC >0.7, from the CT-negative cluster. CL3 had the most severely injured patients with 84% having either moTBI or sTBI whereas

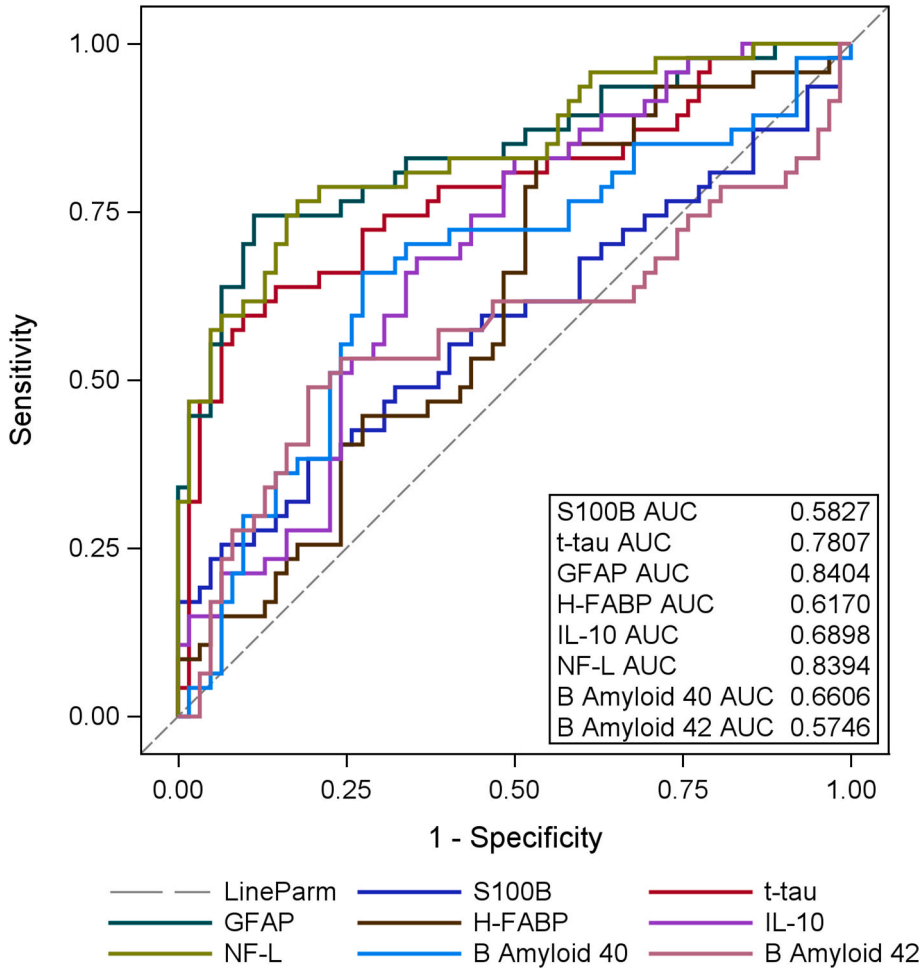


Fig. 3. The ability of the biomarkers to distinguish between ct-negative and the ct-positive cluster CL2, auc-roc curves.

the CT-negative cluster included mainly patients with mTBI (93%). In distinguishing CL2 from the CT-negative cluster, only GFAP and NF-L had good discriminatory ability with an AUC of 0.84 and 0.839, respectively, and t-tau had a reasonable AUC of 0.781. Other biomarkers had poor discriminatory ability.

Some of the patients with mTBI and moTBI in the current study had a focal contusion as their only lesion type. In this cohort (CL1), only NF-L and t-tau reached the AUC of >0.7. However, the cluster is too small for definite conclusions.

As the biomarkers are not specific to brain damage, ISS scores were calculated to estimate the severity of extracranial injuries. There were between 33% and 38% of patients with major extracranial injuries in each cluster. The ISS score was similar in CL2, CL3, and CT-negative cluster with CL1 having somewhat higher extracranial ISS values.

When comparing the biomarker levels between the CT-positive clusters, the levels of Aβ40 differed the most. The levels of GFAP, Aβ40, and Aβ42 were significantly higher in CL3 than in CL1. The diagnostic value of GFAP was highest in detecting patients with mixed intracranial injury, whereas its performance in identifying patients with focal lesions was unexpectedly poor. GFAP levels in the literature have been associated with clinical severity of TBI along with the extent of the intracranial injury (Bazarian et al., 2018; Posti et al., 2016), increasing with age (Gardner et al., 2018). The patients in CL1 had only small focal lesions and thus the lesser severity of the injury might explain the GFAP results as well as the differences in biomarker levels of S100B, Aβ40 and Aβ42 when comparing to CL3. As the cluster CL1 contained only nine patients, the variation between individual patients is pronounced and may distort the results.

S100B has been found to differ according to the injury type with somewhat contradictory results. In one small study, S100B levels were ≤0.20 μg/l in three patients with EDH at admission (Undén et al., 2005). In a larger study, the highest levels of S100B were found in patients with cerebral oedema, the levels being significantly lower with EDH, SDH, SAH and contusions, the lowest levels found with concussion (Wolf et al., 2015). IVH has been shown to increase S100B levels (Whitehouse et al., 2022) as also found in our study with CL3.

Czeiter et al. found GFAP to outperform other biomarkers (S100B, neuron-specific enolase, ubiquitin C-terminal hydrolase L1, NF-L and t-tau) and their combinations or GCS in predicting CT abnormalities and suggest the development of an assay to be used in the clinical setting of TBI triage and decision making (Czeiter et al., 2020).

Large studies have examined the outcomes of different management strategies for the most common traumatic intracranial mass lesions, SDH and tICH. It has been reported that the treatment strategy favouring an aggressive approach of acute operation over initial conservative treatment is not associated with better functional outcome in ASDH (van Essen et al., 2022). For large tICH in moTBI, early operation seems to be beneficial, but in mTBI, conservative initial treatment was associated with better outcome (van Erp et al., 2023). Currently the evacuation decision is based on surgical tradition: clinical and radiological findings. Due to the complexity of the topic, we did not analyze the utility of biomarkers for surgical decision-making in this study. Firstly, our data are too small to analyze this question, and secondly, the confidence intervals of the biomarker levels, especially for sTBI, are large and there are many outliers (Korhonen et al., 2024).

Limitations of the study include small sample and cluster sizes. The

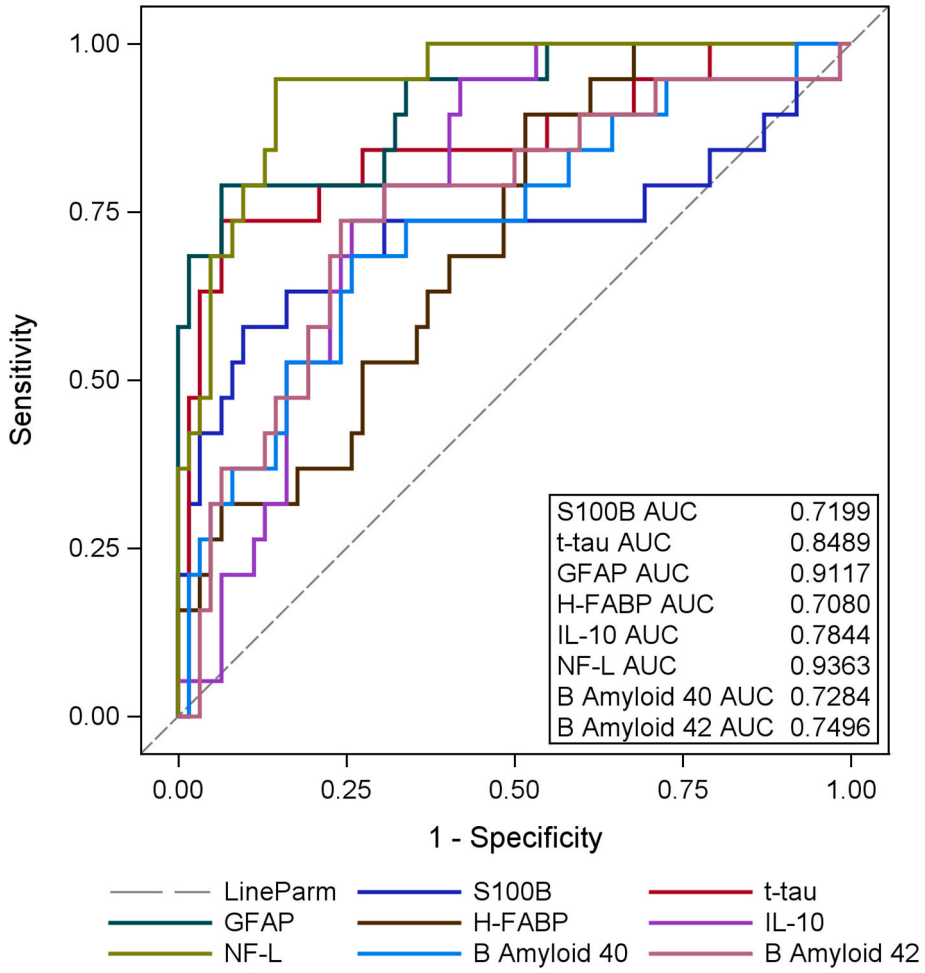


Fig. 4. The ability of the biomarkers to distinguish between ct-negative and the ct-positive cluster CL3, auc-roc curves.

Table 5
Biomarker correlations between the ct-positive clusters 1–3 with the sum of HCTS, age and GOSE.

Spearman Correlation Coefficients, N = 75
Prob > |r| under H0: Rho = 0

	HCTS score	S100B	t-tau	GOSE	Age	GFAP	H-FABP	IL-10	NF-L	B-Amyloid 1_40	B-Amyloid 1_42
HCTS sum	1.000	0.382	0.415	−0.371	0.204	0.491	−0.0274	0.285	0.442	0.277	0.103
p-value		**0.0007**	**0.0002**	**0.0010**	0.0786	**<0.0001**	0.815	**0.0131**	**<0.0001**	**0.0161**	0.382
S100B	0.382	1.000	0.728	−0.433	0.116	0.743	0.401	0.543	0.483	0.361	0.179
p-value	**0.0007**		**<0.0001**	**0.0001**	0.321	**<0.0001**	**0.0004**	**<0.0001**	**<0.0001**	**0.0014**	0.125
t-tau	0.415	0.728	1.000	−0.382	0.0216	0.850	0.247	0.496	0.708	0.192	0.181
p-value	**0.0002**	**<0.0001**		**0.0007**	0.854	**<0.0001**	**0.0323**	**<0.0001**	**<0.0001**	0.0991	0.121
GOSE	−0.371	−0.433	−0.382	1.000	−0.377	−0.401	−0.209	−0.320	−0.409	−0.252	−0.229
p-value	**0.0010**	**0.0001**	**0.0007**		**0.0009**	**0.0004**	0.0714	**0.0051**	**0.0003**	**0.0293**	**0.0480**
Age	0.204	0.116	0.022	−0.377	1.000	0.184	0.135	0.0789	0.315	0.101	0.0871
p-value	**0.0786**	0.321	0.854	**0.0009**		0.115	0.247	0.501	**0.0059**	0.388	0.457
GFAP	0.491	0.743	0.850	−0.401	0.184	1.000	0.141	0.454	0.708	0.244	0.159
p-value	**<0.0001**	**<0.0001**	**<0.0001**	**0.0004**	0.115		0.229	**<0.0001**	**<0.0001**	**0.0349**	0.174
H-FABP	−0.0274	0.401	0.247	−0.209	0.135	0.141	1.000	0.448	0.201	0.0749	0.258
p-value	0.815	**0.0004**	**0.0323**	0.0714	0.247	0.229		**<0.0001**	0.0833	0.523	**0.0252**
IL-10	0.285	0.543	0.496	−0.320	0.0789	0.454	0.448	1.000	0.437	0.122	−0.00307
p-value	**0.013**	**<0.0001**	**<0.0001**	**0.0051**	0.501	**<0.0001**	**<0.0001**		**<0.0001**	0.296	0.979
NF-L	0.443	0.483	0.708	−0.409	0.315	0.708	0.201	0.437	1.000	0.218	0.144
p-value	**<0.0001**	**<0.0001**	**<0.0001**	**0.0003**	**0.0059**	**<0.0001**	0.0833	**<0.0001**		0.0598	0.217
B-Amyloid-1-40	0.277	0.361	0.192	−0.252	0.101	0.244	0.0749	0.122	0.218	1.000	0.313
p-value	**0.016**	**0.001**	0.0991	**0.0293**	0.388	**0.0349**	0.523	0.296	0.0598		**0.0062**
B-Amyloid-1-42	0.103	0.179	0.181	−0.229	0.0871	0.159	0.258	−0.00307	0.144	0.313	1.000
p-value	0.382	0.125	0.121	**0.0480**	0.457	0.174	**0.0252**	0.979	0.217	**0.0062**	

Statistically significant values ($p < 0.05$) are highlighted. GOSE = Glasgow outcome scale – extended, HCTS = Helsinki CT score.

CT-positive patients were clustered according to the outcome associated HCTS variables (Raj et al., 2014). Different combinations of lesions with a large number of patients should be studied for more robust conclusions. The biomarker levels in isolated lesions would have been interesting, but the amount of available data was too small. Second, the patients were not clustered according to the severity of TBI. Since the biomarker levels rise with increasing injury severity, the levels of biomarkers vary depending on the TBI severity in the cluster. In terms for triaging patients for head imaging, biomarker levels in the admission phase in sTBI are clinically not as relevant as in the milder cases, as patients with GCS less than 13 should always have a head CT. We were interested in exploring the biology behind the different types of lesions and it is known that patients with a GCS of 13–15 could have lesions on head CT. Third, the admission blood sampling was obtained within 24 h from the hospitalisation. There were considerable differences in the time intervals between injury and sampling. As the kinetics for each biomarker is different, this can influence their levels, especially for biomarkers with a short half-life such as H-FABP, IL-10, and S100B and on the other hand, for a biomarker with slow kinetics such as NF-L. Variability in admittance is a clinical reality and future studies should clarify how biomarkers perform at different times from injury in various types of TBI. Fourth, the CT-negative patients with TBI served as reference. CT-negative TBI may still be associated with major tissue injury and, accordingly, increased biomarker levels (Richter et al., 2022).

5. Conclusions

All the studied biomarkers adequately discriminated between the CT-negative patients with TBI and the most severely injured cluster, mixed lesions and IVH. Traumatic intracranial findings occur in different combinations and due to the considerable variability, not all combinations may lead to a diagnostic increase in candidate biomarker levels, especially in patients who are still conscious at the time of the examination in the ED. More research on this subject should be conducted in a larger patient population.

CRediT authorship contribution statement

Pia Koivikko: Conceptualization, Methodology, Data curation, Writing – original draft. **Ari J. Katila:** Conceptualization, Methodology, Data curation, Writing – original draft. **Riikka SK. Takala:** Conceptualization, Methodology, Data curation, Writing – review & editing. **Iftakher Hossain:** Conceptualization, Data curation, Writing – review & editing. **Teemu M. Luoto:** Investigation, Writing – review & editing. **Rahul Raj:** Investigation, Writing – review & editing. **Mari Koivisto:** Formal analysis, Writing – review & editing. **Olli Tenovuo:** Data curation, Supervision, Writing – review & editing. **Kaj Blennow:** Resources, Supervision, Writing – review & editing. **Peter Hutchinson:** Supervision, Writing – review & editing. **Henna-Riikka Maanpää:** Data curation, Writing – review & editing. **Mehrbod Mohammadian:** Data curation, Writing – review & editing. **Virginia F. Newcombe:** Supervision, Writing – review & editing. **Jean-Charles Sanchez:** Resources, Supervision, Writing – review & editing. **Jussi Tallus:** Data curation, Writing – review & editing. **Mark van Gils:** Supervision, Writing – review & editing. **Henrik Zetterberg:** Resources, Supervision, Writing – review & editing. **Jussi P. Posti:** Conceptualization, Methodology, Data curation, Investigation, Writing – review & editing.

Ethical approval

The study has been approved by Southwest Finland Hospital District Research Ethics Committee (decision 68/180/2011). Patients or their proxies were given oral and written information about the study and written consent was obtained for all the patients.

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Declaration of competing interest

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