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Blood biomarker outliers and clinical events during intensive care in patients with traumatic brain injury

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ABSTRACT

Introduction: Monitoring and timely clinical assessment are fundamental to treating patients with traumatic brain injury (TBI) in the intensive care unit (ICU). Proactive, individualised treatment is unavailable with the current methods.
Research question: How do outlying blood biomarker levels associate with clinical events or outcome in TBI?
Materials and methods: Glial fibrillary acidic protein (GFAP), neurofilament light (NfL), interleukin-10 (IL-10) and total tau (t-tau) were analysed from blood plasma samples of 70 ICU-treated patients, aged ≥18, with a clinical diagnosis of TBI and an indication for a head CT scan. The blood samples were collected on arrival and on days 1, 2, 3 and 7. The biomarkers were screened for outliers and biomarker values outside Q1-1.5 × interquartile range (IQR) or Q3+1.5 × IQR on any day post-injury were considered outliers. The outlier group was compared with the non-outlier group targeting clinically significant aspects such as high intracranial pressure, seizures/status epilepticus, or mortality/poor outcome. The Glasgow Outcome Scale Extended (GOSE) was evaluated between 6 and 12 months after the injury.

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Results: Difference was found in epileptic activity (n = 7 vs n = 0) and the number of performed decompressive hemicraniectomies (n = 6 vs n = 0) between the outlier and the non-outlier groups, p = 0.015 and < 0.0001, respectively. Patients in the outlier group were also more likely to have a poor outcome (GOSE 1-3) than patients in the non-outlier group, p = 0.011.
Discussion and conclusion: Biomarker outliers seem to associate with clinical events and poor outcome in ICU-treated patients with TBI, possibly due to greater severity of TBI.

Abbreviations

CT	Computed tomography
cEEG	Continuous EEG
ED	Emergency department
EEG	Electroencephalogram
GCS	Glasgow coma scale
GFAP	Glial fibrillary acidic protein
GOSE	Glasgow outcome scale extended
HCTS	Helsinki computed tomography score
ICP	Intracranial pressure
ICU	Intensive care unit
IL-10	Interleukin-10
ISS	Injury severity score
IQR	Interquartile range
LLoD	Lower limit of detection
LLoQ	Lower limit of quantification
moTBI	Moderate TBI
mTBI	Mild TBI
NfL	Neurofilament light
OR	Operating room
SDH	Subdural haematoma
SE	Status epilepticus
sTBI	Severe TBI
TBI	Traumatic brain injury
t-tau	Total tau

1. Introduction

Traumatic brain injury (TBI) is caused by external forces, typically involving direct impact, rapid acceleration/deceleration, and/or rotational motion of the brain. This primary injury triggers pathophysiological changes in the brain leading to secondary injury. Prevention of the secondary injuries is a therapeutic target in TBI treatment (Orr et al., 2024). To date, predicting the occurrence of secondary insults in individual patients is challenging and changes may already set in before the treatment begins. Thus, there is a need to explore more effective preventive strategies (Lazaridis et al., 2019).

Secondary insults may lead to cerebral oedema, which can be identified bedside by raised intracranial pressure (ICP) (Maas et al., 2017). ICP monitoring is recommended for patients with severe TBI (Guidelines for the Management of Severe TBI; Robba et al., 2021). TBI is a complex injury and multimodal monitoring is needed to understand its pathophysiology (Slot et al., 2025). Electroencephalogram (EEG) provides useful information in the more severe TBI as epileptic seizures are observed in up to 5.6% of cases (DeGrauw et al., 2018; Sødal et al., 2022) and they have been associated with poor outcome (Laing et al., 2022). Neurosurgical interventions are required for the timely management of different lesions and secondary injuries (Bullock et al., 2006).

Blood-based biomarkers have been extensively studied in patients with TBI, to aid in diagnostics, characterization, monitoring of patient care and outcome following TBI (Posti and Tenovuo, 2022). Besides TBI, biomarker levels have been identified to increase due to other causes such as old age (Eng et al., 2000; Gardner et al., 2018), extracranial injuries (Posti and Tenovuo, 2022) or prior neurological conditions (Castellani et al., 2019). Very few studies have examined blood biomarker association with clinical factors during treatment. However, biomarkers have been found to be important clinical descriptors of disease trajectories in ICU-treated patients with TBI during the first week of treatment (Åkerlund et al., 2024). Secondary peaks of S100B have been found to correlate with new clinically relevant findings in head computed tomography (CT) scans (Thelin et al., 2014). Glial fibrillary acidic protein (GFAP) breakdown products have been found in substantially higher quantities in patients with mild or moderate TBI who had neurosurgical interventions compared to those who did not (Papa et al., 2012).

Outlier levels of biomarkers have been reported for patients with TBI (Korhonen et al., 2024). Our study investigated outlier levels of GFAP, neurofilament light (NfL), interleukin-10 (IL-10) and total tau (t-tau) in blood occurring the first week after the injury in the ICU cohort of patients with all severities of TBI. Our hypothesis was that the occurrence of clinically significant events linked with secondary injuries, e.g., seizures, increased ICP, and in-hospital mortality/poor outcome might be associated with outlier levels of biomarkers during the first week of ICU treatment. Clinically identifying such an association could prompt additional imaging or continuous monitoring, help to refine thresholds for detecting secondary brain insults, and give information to clinical trial design, particularly regarding timing and biomarker sampling windows.

2. Materials and Methods

2.1. Study population

Patients with all severities of TBI were recruited between November 2011 and October 2013 from 8 a.m. to 10 p.m. (convenience sampling). This study was a part of the EU-funded TBIcare project (Evidence-based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries, Grant Agreement 270259) and it is a retrospective analysis from a prospective observational study. We included all patients with TBI treated in the ICU at Turku University Hospital within this time frame. We included patients with isolated TBI and those with additional extracranial injuries. The Southwest Finland Hospital District Research Ethics Committee (decision 68/180/2011) approved the study.

Inclusion criteria for the study were all patients aged 18 years or older, with a clinical diagnosis of TBI and an indication for acute head CT according to the National Institute for Health and Care Excellence Head Injury Guideline (Eades, 2014) requiring treatment in the ICU. Exclusion criteria were TBI without an indication for head CT, blast-induced or penetrating injuries, prior significant neurological disorders, inability to live independently, chronic SDH or inability to communicate in Finnish. Patients or their representatives received both oral and written information regarding the study, and written consent was required from every patient.

2.2. TBI severity assessment

The severity of TBI was evaluated with the Glasgow Coma Scale (GCS), using the lowest GCS score before potential intubation either at the scene of the injury or in the emergency department (ED). Patients with mild TBI (mTBI) had GCS 13–15, moderate TBI (moTBI) GCS 9–12, and severe TBI (sTBI) GCS 3–8 (Teasdale and Jennett, 1974; Teasdale et al., 2014).

2.3. ISS score

Injury severity score (ISS) (Baker et al., 1974) was calculated for each patient. In addition to total ISS, extracranial and cranial ISS were calculated separately to determine the extent of extracranial injuries. Extracranial ISS $\geq$4 was considered as major injury to ensure all extracranial injuries excluding minor cuts and bruises were accounted for in terms of possible biomarker releasing sources.

2.4. Head computed tomography classifications

Admission CT scans were classified with both Marshall (Marshall et al., 1991) and Helsinki CT scores (HCTS) (Raj et al., 2014) by experienced neuroradiologists and neurosurgeons. Conflicting results were solved in group discussions.

2.5. Biomarker analyses

GFAP, NfL, IL-10 and t-tau concentrations were measured from an EDTA plasma sample collected from the ICU-treated patients on arrival to the hospital, and once a day on days 1, 2, 3 and 7. Plasma was separated from blood samples after a 10-min centrifugation at 10,000 rpm at 4 °C, frozen and stored at −70 °C. GFAP, NfL and t-tau levels were measured with Human Neurology 4-Plex A assay (N4PA) on an HD-1 Single molecule array (Simoa) instrument (Quanterix, Billerica, MA). LLoD (lower limit of detection) for GFAP, NfL and t-tau was 0.221 pg/ml, 0.104 pg/ml, and 0.024 pg/ml, respectively, whereas LLoQ (lower limit of quantification) was 0.467 pg/ml, 0.241 pg/ml, and 0.053 pg/ml, respectively. The dynamic range for GFAP was from 0.987 pg/ml to 725 pg/ml, the range for NfL was from 0.533 pg/ml to 453 pg/ml, and from 0.136 pg/ml to 112 pg/ml for t-tau.

LoD and LLoQ for IL-10 were 0.04 pg/ml and 0.298 pg/ml, respectively, and the dynamic range was 0.0774-317 pg/ml. The K151QUD kit was used to measure IL-10 concentration (Meso Scale Diagnostics, Rockville, MD, USA).

All the samples were above the LLoDs and LLoQs and the kits were used according to the manufacturers' recommendations. Board-certified laboratory technicians used a single batch of reagents in a single experiment cycle to complete the measurements while being blinded to clinical data. All analytes had intra-assay coefficients of variation below 10%, which were tracked using high and low QC samples that were consistent across plates.

2.6. Studied clinical events and outcome

Clinical events studied in association with biomarker outliers were epileptic seizures/status epilepticus (SE), high ICP, neurointerventions used for evacuation of haematomas or to control high ICP, and in-hospital mortality/poor outcome (GOSE 1-3).

2.7. Intracranial pressure assessment

ICP was monitored using intraparenchymal, continuous methods using either Neurovent-PTO (Raumedic AG, Helmbrecht, Germany) or Codman® ICP monitoring system (DePuy Synthes, Wokingham, UK). ICP values were transferred once a minute to the electronic patient record system and the data were collected from the electronic patient record system used in the ICU (Centricity ™ Critical Care 9.9 SP1, General Electric Company). The cut-off value for increased ICP was 20 mmHg. ICP burden, defined as the time spent above ICP values greater than 20 mmHg, was calculated for each patient.

2.8. EEG monitoring

NicoletOne monitoring device (CareFusion Nicolet, San Diego, CA, USA) was used in the ICU to record continuous EEG. An EEG technician placed the Ag-AgCl subcutaneous wire electrodes (Ives EEG Solutions, Manotick, Ontario, Canada) using the international 10-20 system and inspected the electrode contacts daily. Placing all the electrodes was impossible for some patients due to the head injury and for those patients the electrodes were placed either only anteriorly or on one hemisphere. The EEG was recorded to a maximum of 60 h per patient (Tolonen et al., 2018).

2.9. Neurosurgical intervention

The operations performed were categorized from minimal to major operations ranging from insertion of an ICP monitoring catheter to decompressive hemicraniectomy. 0 = no surgery, 1 = inserting an ICP catheter, 2 = ventriculostomy or burr hole for subdural haematoma (SDH), 3 = craniotomy for surgical evacuation of mass lesion, 4 = decompressive hemicraniectomy. Some patients were taken to the operating room (OR) directly after arriving to the hospital and transferred to the ICU after the operation. The rest were operated on during the ICU treatment period once the medical management failed to control the ICP.

2.10. Glasgow outcome scale extended

Glasgow outcome scale extended (GOSE) was used to assess the patients' functional outcome from the injury, ranging from 1 (deceased) to 8 (full recovery) (Wilson et al., 1998, 2021). For all survivors, GOSE was evaluated by an experienced neurologist between 6 and 12 months from the injury.

2.11. Statistical analysis

The biomarker levels were measured for all sampling dates and a level outside Q1-1.5 × IQR or Q3+1.5 × IQR was deemed an outlier. The method has been used previously to define blood biomarker outliers (Korhonen et al., 2024). All the patients with an outlier level biomarker on any biomarker on any sampling day, were included in the outlier group. Continuous variables are reported either as mean (SD) or median (interquartile range) (IQR) and categorical variables are reported as frequency and percentage. Fisher's exact test was used to compare the outlier and non-outlier groups on the EEG data (seizures or status epilepticus) and the ICP data. Furthermore, to assess whether the association between outlier status and seizure-related outcomes was independent of therapy intensity, we performed Firth's bias-reduced logistic regression adjusted for age, sex, and therapy intensity level (TIL). This approach was used to account for the small number of events and complete separation in the data. Multinomial logistic regression including age and sex was used to assess the neurosurgical type with the outliers. The association of biomarker outlier levels with in-hospital mortality or severe disability (GOSE 1-3) was assessed with logistic regression. Group comparisons of biomarker levels across time points were performed using Wilcoxon rank-sum tests, with p-values adjusted for multiple comparisons using the Benjamini–Hochberg method. P-value less than 0.05 was considered statistically significant. Data were analysed using R statistical software (v4.5.1). (R Core Team. R core team, 2021).

Logistic regression models were constructed to evaluate the predictive performance of established clinical risk scores and their extension

with biomarker-derived outlier status. For both IMPACT and CRASH models, published risk probabilities were transformed using the logit function prior to inclusion in regression models to preserve linearity on the log-odds scale.

Base models included the logit-transformed score, age, and sex. Extended models additionally included biomarker outlier status (group). Model discrimination was assessed using receiver operating characteristic (ROC) curves and area under the curve (AUC). Confidence intervals for AUC were estimated using stratified bootstrap resampling with 2000 replicates. Differences between correlated ROC curves were evaluated using bootstrap-based tests.

Given the limited sample size of subjects with GCS $\leq$12 and available IMPACT/CRASH scores (N = 39), results are reported with emphasis on effect sizes and confidence intervals rather than statistical significance.

3. Results

3.1. Biomarker outliers

The measured biomarker outliers are presented in a heat map (Fig. 1) and the difference in biomarker levels between outliers and non-outliers is demonstrated in Fig. 2. Outlier subjects demonstrated significantly higher biomarker levels compared to non-outliers at early time points (days 0 to 2), across all biomarkers (all adjusted p's $<$ 0.02). These differences attenuated over time and were no longer significant by day 7. See Supplemental Table 1 for details. All the outliers were above

Fig. 1. Biomarker outliers' occurrence in individual patients by sampling dates presented in a heat map.

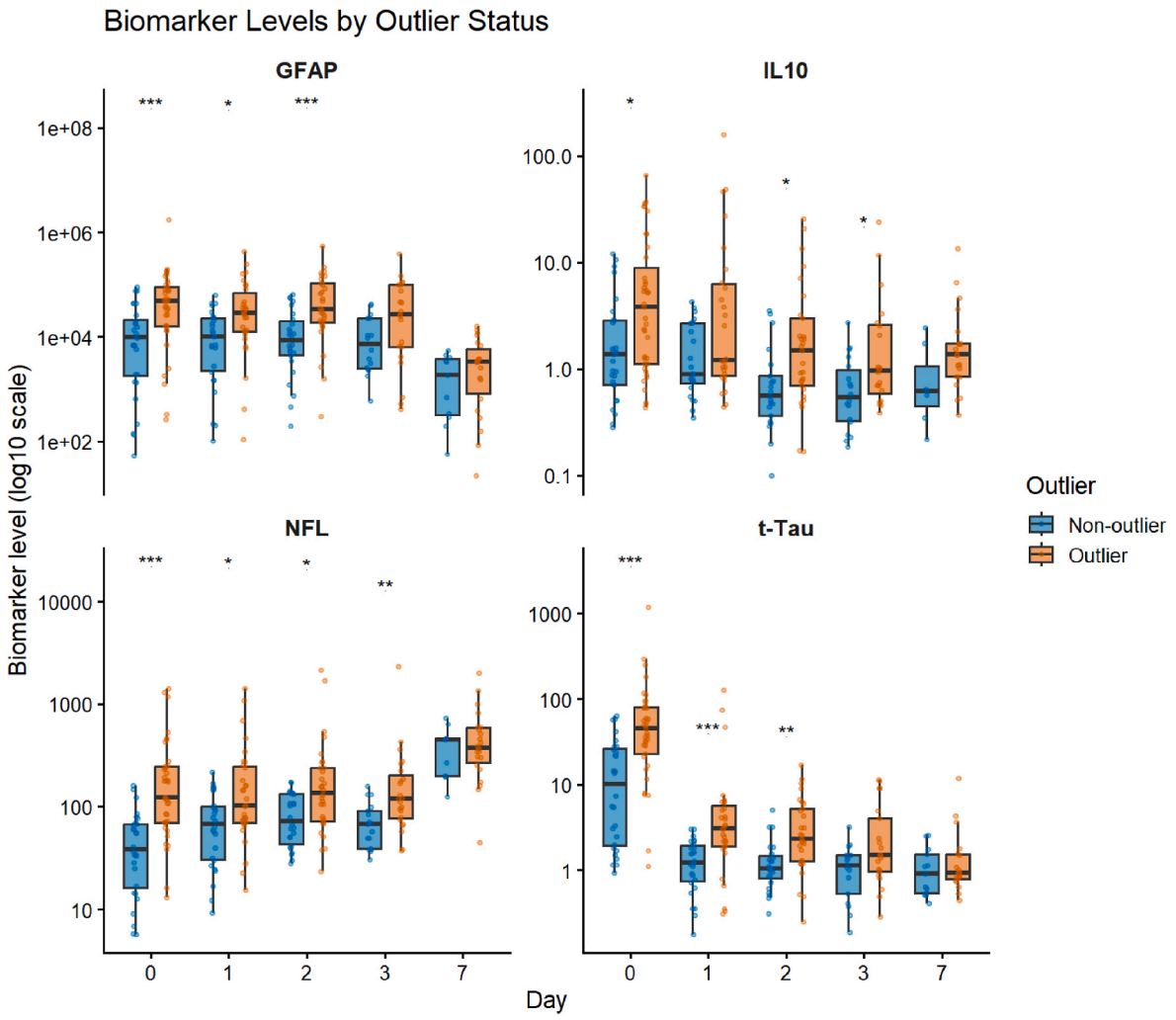

Fig. 2. The difference in biomarker levels between outliers and non-outliers. *, ** and *** indicates statistical significance, further details can be found in Supplementary Table 1.

Q3+1.5 × IQR (Table 1). The patients with outlier levels of biomarkers formed the outlier group.

3.2. Patient demographics

The demographics of the patients are presented in Table 2a–b. The mean age and sex distribution were similar in the outlier (N = 39) and non-outlier (N = 31) groups with majority being men in both groups. There was no significant difference between the two groups in the severity of TBI, e.g. GCS, pupillary reactions, or head CT scans (Marshall or HCTS). There was, however, a significant difference between the outlier and non-outlier groups in both total and cranial injury severity scores (ISS), p = 0.002 and 0.03 respectively, with the patients in the outlier group being more severely injured. In extracranial injuries, however, there was no significant difference between the groups.

3.3. EEG and ICP

All seizure-related events (n = 7) occurred in the outlier group, with none observed in non-outliers (Fisher's exact test, p = 0.015), indicating complete separation. In Firth's bias-reduced logistic regression adjusted for age, sex, and therapy intensity level (TIL), outlier status remained significantly associated with seizure-related outcomes (odds ratio 11.4, 95% CI 1.2–1515, p = 0.032), whereas TIL was not independently associated. There was a significant difference in therapy intensity level between the outliers and non-outliers, p = 0.014. More patients received

Table 1
Biomarker outliers' interquartile range (IQR) per sampling day.

Biomarker	Admission median (IQR)	Day 1 median (IQR)	Day 2 median (IQR)	Day 3 median (IQR)	Day 7 median (IQR)
GFAP (ng/ml)	25.90 (66.52)	17.02 (31.03)	20.49 (49.83)	10.83 (39.61)	3.29 (3.74)
IL-10 (pg/ml)	1.78 (5.06)	1.11 (2.60)	0.80 (1.51)	0.71 (1.02)	1.22 (1.11)
NfL (pg/ml)	71.64 (139.76)	84.26 (98.71)	106.94 (104.38)	93.23 (80.26)	389.26 (332.76)
t-tau (pg/ml)	28.24 (49.70)	1.99 (2.29)	1.43 (2.18)	1.34 (1.12)	0.93 (0.90)

GFAP: N(admission) = 3, N(D1) = 7, N(D2) = 6, N(D3) = 4, N(D7) = 4.
IL-10: N(admission) = 9, N(D1) = 6, N(D2) = 6, N(D3) = 4, N(D7) = 4.
NfL: N(admission) = 7, N(D1) = 5, N(D2) = 5, N(D3) = 5, N(D7) = 2.
t-tau: N(admission) = 4, N(D1) = 4, N(D2) = 5, N(D3) = 6, N(D7) = 3.

Table 2a
Demographics of the study patients.

Variable	Outlier group (N = 39)	Non-outlier group (N = 31)	p-value
Age, years, mean (SD)	51.17 (20.25)	47.29 (18.19)	0.407[a]
Sex, N (%, Female)	6 (15.38)	4 (12.9)	0.768[b]
GCS severity, N (%)			0.467[b]
Mild (13-15)	13 (33.33)	15 (48.39)	
Moderate (9-12)	11 (28.21)	10 (32.26)	
Severe (3-8)	15 (38.46)	6 (19.35)	
Pupil reactivity, N (%)			0.228[c]
Reactive	23 (58.97)	20 (64.52)	
Sluggish	1 (2.56)	1 (3.23)	
Unreactive	12 (30.77)	4 (12.9)	
Missing	3 (7.69)	6 (19.35)	
CT findings			
CT-neg	6	3	
CT-pos	25	36	
Marshall CT score, N (%)			0.348[c]
1	3 (7.69)	6 (19.35)	
2	7 (17.95)	9 (29.03)	
3	5 (12.82)	3 (9.68)	
4	0	0	
5	19 (48.72)	9 (29.03)	
6	5 (12.82)	4 (12.9)	
Helsinki CT score, N (%)			0.337[c]
3	0	1 (3.23)	
2	0	0	
1	0	1 (3.23)	
0	3 (7.69)	3 (9.68)	
1	0	0	
2	1 (2.56)	3 (9.68)	
3	1 (2.56)	3 (9.68)	
4	3 (7.69)	4 (12.9)	
5	7 (17.95)	3 (9.68)	
6	4 (10.26)	1 (3.23)	
7	4 (10.26)	0	
8	2 (5.13)	0	
9	1 (2.56)	0	
10	4 (10.26)	2 (6.45)	
11	0	0	
12	1 (2.56)	1 (3.23)	
13	0	0	
14	0	0	
Missing	8 (20.51)	9 (29.03)	
Therapy intensity level (TIL), N(%)			0.014[c]
No intubation or sedation (tier 0)	2 (5.13)	7 (22.58)	
Intubation or sedation only (tier 1)	25 (64.1)	22 (70.97)	
Hyperosmolar therapy (tier 2)	6 (15.38)	2 (6.45)	
hypothermia or decompressive hemicraniectomia during ICU treatment (tier 3)	6 (15.38)	0	

[a]Student's t-test; [b]Chi-square test; [c]Fisher's exact test; [d]Mann-Whitney *U* test. GCS = Glasgow coma score.

Table 2b
Demographics of the study patients.

Variable	Outlier group (N = 39)	Non-outlier group (N = 31)	p-value
ISS total, median (IQR)	25 (18)	17 (16)	**0.002**[d]
ISS cranial, median (IQR)	16 (16)	9 (12)	**0.03**[d]
ISS extracranial, median (IQR)	8 (18)	2 (8)	0.242[d]
Neurosurgery, N (%)			0.178[c]
ICP	6 (15.38)	5 (16.13)	
Craniotomy	13 (33.33)	9 (29.03)	
Hemicraniectomy	6 (15.38)	0	
Ventriculostomy, trepanation	3 (7.69)	3 (9.68)	
No operations	11 (28.21)	14 (45.16)	
GOSE, N (%)			**0.033**[c]
1	13 (33.33)	3 (9.68)	
2	0	0	
3	6 (15.38)	2 (6.45)	
4	5 (12.82)	2 (6.45)	
5	5 (12.82)	5 (16.13)	
6	4 (10.26)	5 (16.13)	
7	5 (12.82)	6 (19.35)	
8	1 (2.56)	5 (16.13)	
Missing	0	3 (9.68)	
EEG, N (%)			**0.037**[c]
No seizures or SE	32 (82.05)	31 (100)	
Seizures	5 (12.82)	0	
Status epilepticus	2 (5.13)	0	
ICP burden, N (%)			0.186[b]
<20 mmHg	29 (74.36)	27 (87.1)	
>20 mmHg	10 (25.64)	4 (12.9)	
In-hospital mortality, N (%)			**0.018**[c]
Yes	10 (25.64)	1 (3.23)	
No	29 (74.36)	30 (96.77)	
Presence of major extracranial injury, N (%)			0.156[b]
Yes	23 (58.97)	13 (41.94)	
No	16 (41.03)	18 (58.06)	

[a]Student's t-test; [b]Chi-square test; [c]Fisher's exact test; [d]Mann-Whitney *U* test. EEG = electroencephalogram; GOSE = Glasgow coma scale extended; ICP = intracranial pressure; SE = status epilepticus. The significant p-values are bolded.

Table 3
Outlier association to neurosurgical procedures.

Surgery type	Predictor	Std. Error	Odds Ratio	p-value
Craniotomy	Any_iqr	0.61	1.77	0.35
	Age	0.017	1.01	0.60
	Sex = male	1.00	0.469	0.45
Hemicraniectomy	Any_iqr	0.85	≫ 100,000	**< 0.0001**
	Age	0.029	0.95	0.097
	Sex = male	1.31	0.074	**0.047**
Ventriculostomy	Any_iqr	0.92	1.33	0.76
	Age	0.025	0.98	0.37
	Sex = male	0.66	≫ 100,000	**< 0.0001**
ICP monitoring	Any_iqr	0.77	1.97	0.38
	Age	0.021	0.97	0.11
	Sex = male	1.12	0.53	0.57

Any_iqr = any outlier biomarker at any sampling day. The significant p-values are bolded.

hyperosmolar therapy (tier 2) in the outlier group and hypothermia or decompressive craniectomy (tier 3) was administered only in the outlier group. There was no difference in ICP burden between the groups within our patient population.

3.4. Neurosurgical interventions

No significant difference was found between the outlier and the non-outlier groups in the total amount of neurosurgical interventions performed (Table 2b). Nine (12.9%) patients had more than one neurosurgical intervention performed. When assessing the different procedure types separately (Table 3), there was a strong positive association between decompressive hemicraniectomy and the outlier group, $p < 0.0001$. The patients undergoing decompressive hemicraniectomy (N = 6) all belonged to the outlier group. Three patients were operated promptly after hospital admittance, three later during the ICU treatment period. Almost all craniotomies (N = 19, 86%) were performed either on the day of the injury or the next day regardless of which group they belonged to, outlier or non-outlier. One patient in the hemicraniectomy group had SE, craniotomy was performed to four (57.1%) other patients with seizures or SE.

3.5. In-hospital mortality

Table 4 shows the results for outliers and their association with in-

Table 4
Biomarker outliers' association with in-hospital mortality or severe disability.

Age group	Odds Ratio for GOSE 1-3 (any_iqr)	95% CI	p
<65	3.66	1.03 to 15.48	0.056
≥65	7.50	0.80 to 175.66	0.113
All ages	4.37	1.46 to 15.15	**0.012**

The significant p-values are bolded.

hospital mortality or poor outcome (GOSE 1-3). When the patients are evaluated as one group, the result is significant, p = 0.012. When the patients are dichotomised into age groups, <65 and ≥ 65-year-old, the results remain insignificant, p = 0.056 and 0.113, respectively.

Fig. 3 shows the comparison of IMPACT and CRASH prediction models with the addition of outliers. The base IMPACT mortality model demonstrated good discrimination (AUC = 0.81, 95% CI: 0.65 to 0.94). Addition of biomarker outlier status did not materially improve performance (AUC = 0.81, 95% CI: 0.65 to 0.93; p = 0.90). For prediction of favourable outcome, the base IMPACT model showed moderate discrimination (AUC = 0.71, 95% CI: 0.53 to 0.86). Inclusion of outlier status increased the AUC to 0.79 (95% CI: 0.62 to 0.93), representing a noticeable improvement in discrimination, although this did not reach statistical significance (p = 0.17). The CRASH mortality model demonstrated good baseline discrimination (AUC = 0.80, 95% CI: 0.63 to 0.94), which remained largely unchanged after inclusion of outlier status (AUC = 0.81, 95% CI: 0.65 to 0.94; p = 0.65). For favourable outcome prediction, the CRASH model showed moderate discrimination (AUC = 0.72, 95% CI: 0.54 to 0.86). Addition of outlier status increased the AUC to 0.78 (95% CI: 0.62 to 0.91), indicating improved classification performance, though this difference was not statistically significant (p = 0.23). Across models, incorporation of biomarker-derived outlier status showed a consistent trend toward improved

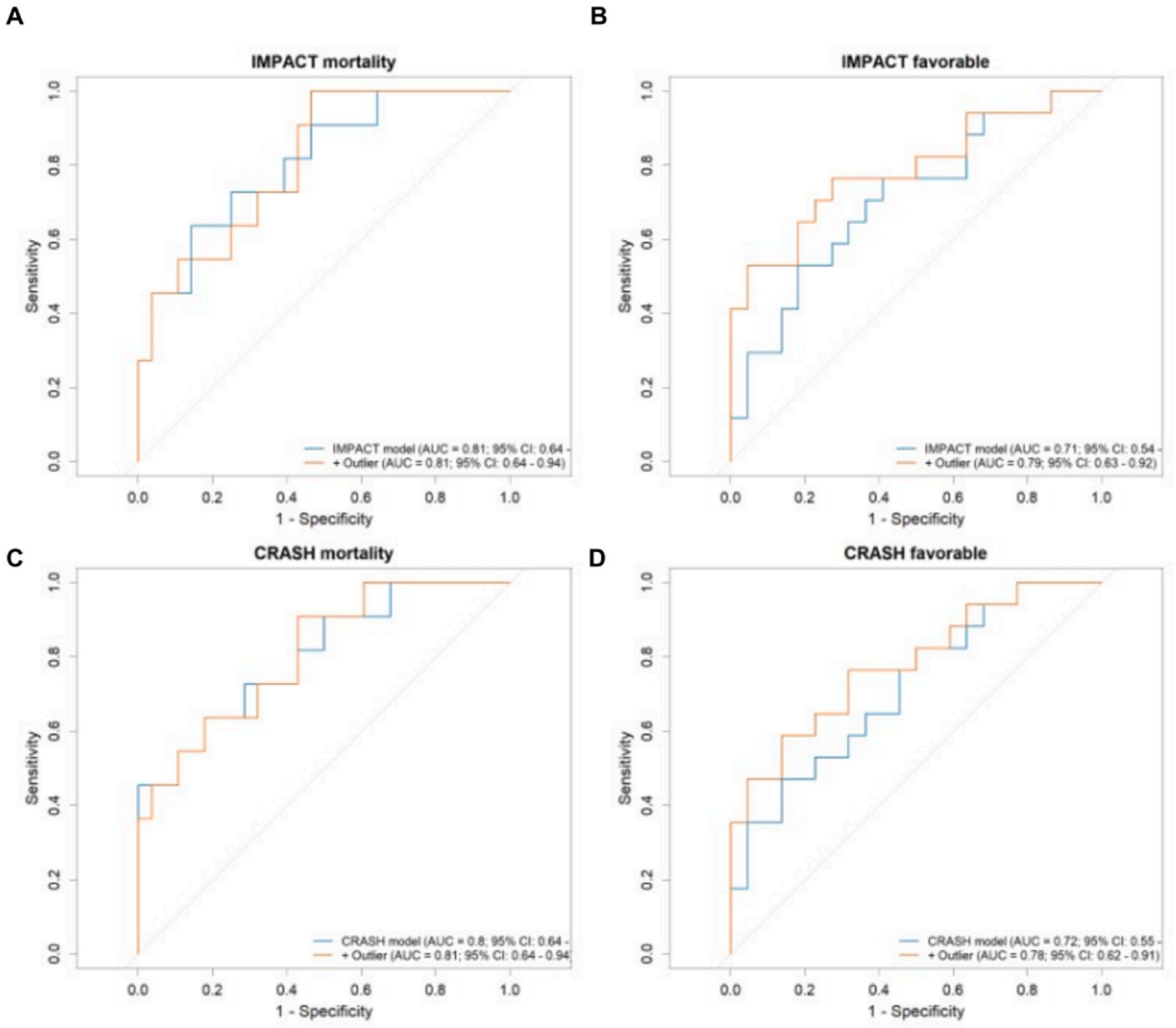

Fig. 3. Receiver operating characteristic (ROC) curves comparing base clinical models (IMPACT or CRASH) with extended models incorporating biomarker-derived outlier status for prediction of mortality and favourable outcome. Clinical risk scores were logit-transformed before inclusion in logistic regression models. Orange lines represent extended models; blue lines represent base models. Area under the curve (AUC) values with 95% confidence intervals were estimated using stratified bootstrap resampling (2000 replicates). Differences between models were assessed using bootstrap-based tests for correlated ROC curves. While the addition of outlier status resulted in a nominal increase in AUC for favourable outcome prediction, these differences did not reach statistical significance (p > 0.05).

discrimination for favourable outcome prediction, while offering limited additional value for mortality prediction, although these findings should be interpreted cautiously given the small sample size.

4. Discussion

The aim of our study was to examine the association of biomarker outliers (GFAP, NfL, IL-10, t-tau) as a group with clinically significant events and outcome during the first week of treatment in the ICU. Markedly elevated blood biomarker values in patients with TBI are real findings that likely reflect exceptionally extensive tissue injury or systemic damage that are not reflected with median values. Main findings of the study were that epileptic seizures and status epilepticus were present only in the outlier group. Also, decompressive hemicraniectomies were performed only in the patients in the outlier group. The patients in the biomarker outlier group were significantly more likely to have a poor outcome (GOSE 1-3) than the patients in the non-outlier group.

Several blood biomarker levels increase with TBI (Whitehouse et al., 2025), but they may also be elevated due to other causes. Circulating GFAP levels in healthy volunteers increases with age (Eng et al., 2000; Gardner et al., 2018) as well as NfL and tau levels, which may also be increased by extracerebral injuries (Posti and Tenovuo, 2022). Elevated tau levels are also associated with prior neurological conditions (Castellani et al., 2019). Early hypotension or a combination with hypoxia in TBI has been observed to elevate NfL, tau and S100B (Robba et al., 2024).

Limited research exists concerning the outlier levels of blood biomarkers in TBI. Admission biomarker data for GFAP, NfL, IL-10 and t-tau in patients with mo/sTBI has been examined for outliers (Korhonen et al., 2024). Very severely injured patients were found to have exceptionally high GFAP values, whereas IL-10 outliers seemed to be caused by severe extracranial injuries, i.e., multi-trauma. Older age was associated with higher NfL levels, and pre-existing neurological conditions could raise both NfL and t-tau. Pre-existing neurological conditions and old age explained the high GFAP and NfL levels in the orthopaedic controls, whereas IL-10 was raised by multi-trauma (Korhonen et al., 2024). A few examples of elevated t-tau were found to be caused by multi-trauma, but the cause for most t-tau outliers in the orthopaedic group remained without an obvious reason. High GFAP was associated with poor outcome (Korhonen et al., 2024).

Patients in our study represented all severities of TBI. Previous studies have shown that less than half of the patients with TBI treated in the ICU are sTBI (Huijben et al., 2020). More than a third are patients with mTBI treated in the ICU, because of severe extracranial injuries (Huijben et al., 2020) or because of a risk of neurological or clinical decline (Bonow et al., 2019). This is consistent with our patient profile. In our study, there was no significant difference in GCS or extracranial ISS between the outlier and the non-outlier groups, however there was a significant difference in the total ISS and the cranial ISS scores with the cranial ISS score likely to cause the difference in the total ISS score. Thus, concluding from these scores, the main difference in the injury profile between the outlier and the non-outlier groups, was the head injuries suggesting that the patients in the outlier group had more severe brain injuries. This is also supported by the more often used tier 2 and tier 3 therapies in the outlier group.

The incidence of early posttraumatic seizures after TBI has been reported to be from 0.4% in studies from the USA (DeGrauw et al., 2018; Majidi et al., 2017) up to 5.6% in a Norwegian study (Sødal et al., 2022) with differences in the definitions and data collection or reporting methods probably explaining the gap. However, previous studies have found seizures after TBI to be associated with longer ICU stays and poor outcome including increased long-term mortality (Laing et al., 2022) making this subject an important study target. Factors, such as prior alcohol misuse, SDH and brain contusions, have been identified as independent risks of seizures after mo/sTBI (Sødal et al., 2022; Majidi et al., 2017; Wiedemayer et al., 2002). However, TBI severity has also been found to contribute to the occurrence of seizures (Laing et al., 2022). In our study population, there was a significant difference in the epileptic activity between the outlier group and the non-outlier group. Since the outlier group patients had more severe injuries, the epileptic seizures most likely reflect the severity of TBI. In addition, the patients in the outlier-group had a poorer outcome, concurring with the previous results of Laing et al. (2022)

ICP monitoring is considered a standard in TBI care when suspecting possible increase in ICP and is associated with better outcome with the more severe TBI (Slot et al., 2025). The best method for monitoring ICP is invasive (Slot et al., 2025). We explored the association of biomarker outlier levels with raised ICP. We found no difference in the ICP burden between the outlier and non-outlier groups. However, as high ICP needs to be promptly treated, ventriculostomies and decompressive hemicraniectomies were performed to lower the ICP in patients where medical management was insufficient. This could explain the lack of differences in ICP burden between the two study groups.

We examined the different types of neurosurgical operations performed on the study patients. A strong positive association was found with the outlier status; however, the interpretation should be done with caution as the number of patients is small. No significant effect for age across categories was found except a borderline association in decompressive hemicraniectomy ($p = 0.097$). For craniotomy, none of the predictors reached statistical significance. Several patients had more than one procedure. Most patients with seizures ($N = 5$, 74.1%) had a prior operation, with one patient undergoing a decompressive hemicraniectomy while the rest of the patients underwent craniotomies.

We found that there was a significant group difference in the in-hospital mortality or poor outcome between the outlier and non-outlier groups. The results suggest that across all ages, patients with biomarker outliers were significantly more likely to have a poor outcome (GOSE 1-3) than patients with the non-outliers. When divided into age groups with a cut-off at 65 years, 95% CI remains very wide, which is probably due to the small number of patients and thus the result is not reliable. Previous studies have found that the levels of biomarkers associate with the severity and extent of lesions in TBI, where a greater injury burden will cause a higher rise to the biomarker values (Whitehouse et al., 2022). As the outcome in our outlier patient group was poorer than in the non-outlier group, this could suggest that the patients in this group were more seriously injured. This is supported also by higher ISS values in the outlier patient group.

We evaluated whether incorporation of biomarker-derived outlier status improves the predictive performance of established clinical prognostic models in traumatic brain injury. While the addition of outlier status did not meaningfully enhance discrimination for mortality prediction, it consistently improved model performance for favourable outcome across both IMPACT (Steyerberg et al., 2008) and CRASH (Perel et al., 2008) frameworks. This pattern suggests that biomarker-derived features may capture aspects of recovery potential that are not fully reflected in traditional clinical risk scores, which are primarily optimized for predicting mortality. The observed improvements in AUC for favourable outcome, although not statistically significant, were consistent in direction and magnitude, supporting a potential role for biomarker integration in refining outcome prediction. Importantly, the lack of statistical significance is likely influenced by the limited sample size, as reflected by the wide confidence intervals. Therefore, these findings should be interpreted as hypothesis-generating and warrant validation in larger, independent cohorts. This pattern suggests that biomarker-derived features may capture aspects of recovery potential that are not fully reflected in traditional clinical risk scores, which are primarily optimized for predicting mortality.

All the biomarkers (GFAP, NfL, IL-10, t-tau) in our study had outlier biomarker values. The occurrence of the outliers was spread across all sampling days, and no robust finding for any biomarker or any clinical parameter could be identified. The sample size was too small to make a

more detailed analysis. The extent to which neurosurgical procedures influence these biomarker levels remains unclear creating a confounder in clinical practise for biomarker outlier use as many patients have an operation promptly after admission. As seizures, possibly unnoticed nonconvulsive, also elevate the biomarker values, there are many confounding factors to using biomarker outliers as clinical predictors.

There are limitations in our study. First, the analysis was a retrospective single-centre study and the available patient data was gathered from the electronic hospital data files. Second, the number of study patients remained relatively small. Third, the blood samples were collected only once a day, and all patients did not have a biomarker sample from all the collection dates thus causing missing values in the biomarker data. Fourth, due to small sample size, robust analysis for individual evaluation per biomarker or per day was not possible, instead our analyses were based on group evaluations. The small number of patients also affected our possibility to study the effect of the surgical treatment on biomarker levels. The number of patients also affects the interpretation of hemicraniectomy data as the analysis confirms association but has no discriminative or predictive value. Fifth, initially our study patients were classified to be all severities, from mTBI to sTBI, however, this classification was not considered within our evaluations. Sixth, as the study design was retrospective and additional data were unavailable, monitoring of lesion progression on CT was not possible due to missing control head CTs for several patients. Seventh, detailed sedation data was not available from the study period preventing further analysis on the level of sedation regarding seizures or SE.

5. Conclusions

Biomarker outliers were associated with clinically significant events associated with secondary injuries and poor outcome. This finding, however, may be due to greater severity of TBI in the outlier group. Larger studies with a robust plan for blood sampling together with multimodal neuromonitoring and head CT controls should be conducted to verify the results. The temporal relationship between high biomarkers and clinical events requires further studies.

CRediT authorship contribution statement

Pia Koivikko: Conceptualization, Methodology, Data Curation, Writing – original draft. **Jussi P. Posti:** Conceptualization, Methodology, Data Curation, Investigation, Writing - Review & Editing. **Iftakher Hossain:** Conceptualization, Data Curation, Writing - Review & Editing. **Mehrbod Mohammadian:** Data Curation, Writing - Review & Editing. **Olli Tenovuo:** Data Curation, Supervision, Writing - Review & Editing. **Peter Hutchinson:** Supervision, Writing - Review & Editing. **Ari J. Katila:** Methodology, Data Curation, Writing - Review & Editing. **Henna-Riikka Maanpää:** Data Curation, Writing - Review & Editing. **David K. Menon:** Supervision, 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. **Riikka SK. Takala:** Conceptualization, Methodology, Data Curation, Writing - Review & Editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2026.106078.

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