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Diagnostic and prognostic utility of rapid point-of-care GFAP and UCH-L1 testing in traumatic brain injury

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Timely identification of traumatic intracranial injuries and prediction of long-term outcomes remain critical challenges in traumatic brain injury (TBI) care. Glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) have emerged as promising biomarkers for the diagnosis and prognosis of TBI. This study evaluated the diagnostic and prognostic utility of a novel point-of-care testing (POCT) platform in a real-world emergency setting. We conducted a prospective, multicenter case–control study across five emergency departments. A total of 200 TBI patients with CT-identifiable intracranial injuries (CT + TBI) and 200 TBI patients without intracranial injuries (CT– TBI), all presenting within 24 h of injury, were enrolled. Serum GFAP and UCH-L1 levels were measured using a rapid multiplex POCT platform (VEUPLEX™ TBI Assay). Diagnostic performance metrics were calculated. Associations between biomarker levels and 6-month survival and neurological outcomes were assessed using multivariable logistic regression among the CT + TBI patients. Median serum concentrations of both GFAP and UCH-L1 were significantly higher in the CT + TBI group compared to the CT– TBI group (medians [IQR] for GFAP: 129.95 [30.83–823.41] vs. 5.27 [3.48–6.14] pg/mL; UCH-L1: 262.23 [75.88–1170.04] vs. 58.49 [20.91–165.69] pg/mL; both $p < 0.001$). The combined biomarker assay demonstrated high sensitivity (0.910; 95% CI, 0.870–0.950) and negative predictive value (0.878; 95% CI, 0.825–0.931) for detecting CT-confirmed intracranial injuries. For long-term outcomes, the combined assay was significantly associated with reduced 6-month survival (AOR: 0.09; 95% CI, 0.01–0.84). Elevated UCH-L1 alone was significantly associated with decreased odds of favorable neurological recovery (AOR: 0.17; 95% CI, 0.05–0.62). Rapid bedside measurement of GFAP and UCH-L1 enables early detection of intracranial injury and is associated with long-term outcomes following TBI. The combined assay provides complementary diagnostic and prognostic information, supporting its potential role in acute TBI evaluation and risk stratification.

Keywords Traumatic brain injury, Biomarker, GFAP, UCH-L1, Intracranial hemorrhage, Prognosis, Point-of-care testing

Traumatic brain injury (TBI) is a major global public health concern, characterized by high incidence and mortality rates[1]. It is estimated that over 28 million people are diagnosed with TBI annually, and the condition accounts for approximately 8.1 million years of life lived with disability (YLDs)[2]. Beyond the individual burden, TBI imposes significant socioeconomic costs due to long-term care requirements, loss of productivity, and substantial healthcare expenditures.

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Numerous efforts have been made to improve outcomes in TBI. However, the inherently heterogeneous nature of the condition—including differences in initial levels of consciousness, a broad spectrum of neurological presentations, variations in the type and extent of intracranial hemorrhage, and the presence of concurrent extracranial injuries—leads to substantial variability in clinical prognosis. This heterogeneity presents major challenges for clinicians in the rapid and accurate assessment of TBI patients, including neuroimaging interpretation and prognostication, thereby underscoring the need for more precise, rapid, and objective diagnostic tools[3].

Recent large-scale cohort studies, such as the TRACK-TBI study, have demonstrated that day-of-injury plasma concentrations of GFAP and UCH-L1 are not only associated with intracranial injury but also provide prognostic information for long-term outcomes, including 6-month mortality and unfavorable neurological recovery[4]. However, although these findings suggest prognostic potential, the utility of these biomarkers across the full spectrum of TBI severity and in real-world emergency settings remains incompletely understood.

Head computer tomography (CT) is the primary imaging modality for evaluating traumatic intracranial injuries, with an estimated 20 million scans performed annually in the United States[5]. While effective at detecting clinically significant hemorrhages, its widespread use raises concerns about radiation exposure[6], unnecessary utilization of emergency department (ED) resources, and rising healthcare costs[7,8]. Moreover, the requirement for specialized personnel and infrastructure can lead to delays in imaging, which have been linked to prolonged time to diagnosis and worse neurological outcomes in TBI patients[9]. To overcome these limitations, extensive research has focused on developing blood-based biomarkers to improve the rapid diagnosis and risk stratification of intracranial injuries following TBI[10–12]. Since the U.S. Food and Drug Administration (FDA) approved the first blood-based test measuring GFAP and UCH-L1 for the evaluation of mild TBI in 2018, several biomarker-based diagnostic tools have been introduced into clinical practice[13]. Comprehensive reviews have set out the biological rationale for this biomarker pair, describing GFAP as an astroglial intermediate filament protein and UCH-L1 as a neuron-specific deubiquitinating enzyme, both of which circulate at low concentrations in health and rise rapidly after brain injury, and situating them within the broader panel of candidate TBI biomarkers that includes S100B, neurofilament proteins, tau, and autoantibody markers[14]. A parallel review of their translational trajectory has documented how this tandem pair progressed from laboratory discovery to the first marketed in vitro diagnostic blood test for the brain, and has emphasised that analytical performance, sample matrix, and intended use are central determinants of how such assays perform in practice[15]. However, current platforms face notable limitations, including prolonged turnaround times and the inability to support multiplex testing. Given that rapid diagnosis and timely intervention are closely linked to neurological outcomes in TBI, these limitations hinder the effective use of such diagnostic methods in acute care settings, where timely and comprehensive assessment is critical.

This study utilized a highly sensitive point-of-care testing (POCT) platform capable of rapidly and simultaneously quantifying serum GFAP and UCH-L1 levels at the bedside. The primary objective was to evaluate the diagnostic performance of this POCT platform in detecting CT-identifiable intracranial abnormalities in patients with TBI. Additionally, we investigated the relationship between early biomarker concentrations and long-term clinical outcomes among patients with CT-confirmed intracranial injuries, thereby extending the potential utility of serum biomarkers from acute diagnostic support to prognostic stratification.

Methods

Study design and sample size estimation

This prospective, multicenter case–control study was conducted to validate the performance of a blood-based biomarker test combining GFAP and UCH-L1 in predicting CT-detected intracranial injuries within 24 h of TBI. The study was conducted between June 2019 and July 2023 at the EDs of five tertiary academic hospitals across Korea.

Sample size estimation was based on data from a prior pilot study with a similar design, in which serum concentrations of GFAP and UCH-L1 were measured using mass spectrometry in patients with and without CT-confirmed intracranial hemorrhage. The null hypothesis assumed an area under the receiver operating characteristic curve (AUROC) of 0.5 for the combined biomarkers, while the alternative hypothesis, based on pilot findings, assumed an AUC of 0.64. Sample size calculation was performed using the power.roc.test() function from the caret package in R, with a two-sided alpha level of 0.01, a statistical power of 0.90, and a 1:1 case-to-control ratio (kappa = 1). To compensate for the small sample size in the pilot study and improve the robustness of the estimate, resampling techniques—including 10-fold 3-round cross-validation and bootstrap resampling (N = 1,000)—were applied to the distribution of GFAP and UCH-L1 values.

Based on this approach, the minimum required sample size was determined to be 130 cases and 130 controls. Considering an anticipated dropout rate of approximately 35%, the final target enrollment was set at 200 patients with CT-identifiable intracranial injury and 200 controls.

This study was conducted and reported in accordance with the STARD 2015 (Standards for Reporting Diagnostic Accuracy Studies) guidelines. Statistical reporting followed established recommendations for transparency and completeness in medical research[16].

Study population

All patients aged 18 years or older who presented to the participating EDs within 24 h of TBI were prospectively screened and enrolled after obtaining informed consent from the patient or their legal representative. Patients were classified into either the case or control group. The case group included patients with radiologically confirmed intracranial injuries—such as intracranial hemorrhage or diffuse axonal injury—on CT or MRI. The control group comprised TBI patients with no evidence of intracranial injury on neuroimaging.

The control group comprised patients with traumatic brain injury who presented to the participating emergency departments during the study period and had no evidence of intracranial injury on neuroimaging. Controls were not individually matched to cases at enrollment.

Exclusion criteria included penetrating brain injury, terminal illness, pre-existing neurological or psychiatric conditions with cognitive impairment, pregnancy, and transfer to a study ED after undergoing surgical intervention at a referring hospital. Patients with missing data on serum GFAP or UCH-L1 levels or unknown clinical outcomes were also excluded.

Study outcomes

The primary outcomes of this study were the sensitivity and negative predictive value (NPV) of the GFAP and UCH-L1 assay for detecting intracranial injuries identifiable on head CT. Additionally, the assay's specificity, positive predictive value (PPV), and both the positive (LR +) and negative (LR–) likelihood ratios were calculated for the identification of CT-confirmed intracranial injuries.

To evaluate the prognostic utility of the assay, we also examined the association between early biomarker levels and 6-month clinical outcomes, including mortality and neurological function. Neurological recovery was assessed using the Glasgow Outcome Scale (GOS), a validated tool for evaluating functional status after TBI. The GOS ranges from 1 to 5, with the following categories: 1 = death, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = good recovery. A favorable outcome was defined as a GOS score of 4 or 5.

Sample preparation and serum biomarker analysis

Venous blood samples were collected in serum-separating tubes (SSTs) and allowed to clot at room temperature (15 °C to 25 °C) for approximately one hour before centrifugation at 3,000 rpm for 10 min. The resulting serum was aliquoted into collection tubes, labeled with unique encrypted identifiers, and transported by an accredited courier to a designated biorepository. All samples were stored at – 80 °C until analysis.

Biomarker quantification was conducted in a blinded manner at Seoul National University Hospital using the VEUPLEX™ TBI Assay, according to the manufacturer's standardized protocol. The VEUPLEX™ TBI Assay is a single-use test cartridge compatible with the VEUDx system, a fully automated in vitro diagnostic analyzer. This assay enables simultaneous quantification of GFAP and UCH-L1 concentrations from a single 50 µL serum sample within one hour. An integrated control system measures two predefined concentrations to verify cartridge quality.

The assay's measurement ranges were 1.56–200 pg/mL for GFAP and 3.13–400 pg/mL for UCH-L1. The limits of detection (LOD) were 0.39 pg/mL for GFAP and 0.78 pg/mL for UCH-L1; the limits of quantification (LOQ) were 1.56 pg/mL and 3.13 pg/mL, respectively[17]. All samples were diluted four-fold prior to analysis (50 µL serum mixed with 150 µL buffer), and reported concentrations were corrected to reflect the original (undiluted) sample concentration. Accordingly, the effective measurement ranges for the original samples were 6.24–800 pg/mL for GFAP and 12.52–1,600 pg/mL for UCH-L1. The assay was validated in accordance with the Clinical and Laboratory Standards Institute (CLSI) guideline EP17-A2.

Determination of cutoff values

Cutoff values for GFAP and UCH-L1 were determined using a data-driven approach informed by both prior validation studies and regulatory considerations. A total of 58 samples (29 CT-positive and 29 CT-negative) were selected from three independent clinical evaluation datasets to reflect a diverse clinical population.

ROC curve analysis was conducted to identify candidate thresholds. Considering that sensitivity was the primary endpoint for clinical validation, cutoff values were selected to ensure high sensitivity, even at the expense of reduced specificity. In practice, thresholds corresponding to sensitivity levels approximately 5–10% below the target sensitivity were chosen to balance robustness and clinical applicability.

Based on this process, cutoff values were set at 17 pg/mL for GFAP and 101 pg/mL for UCH-L1. A combined rule was applied, whereby a test result was considered positive if either biomarker exceeded its respective cutoff, in order to enhance rule-out performance. A detailed comparison of analytical performance characteristics and cutoff values, including platform-specific parameters, has been provided in the Supplementary Materials (Table S1 and Figure S1).

Measurements and variables

The primary exposure variables were the serum concentrations of GFAP and UCH-L1. Based on manufacturer-defined thresholds, GFAP ≥ 17 pg/mL and UCH-L1 ≥ 101 pg/mL were considered positive. Participants were categorized as biomarker-positive or -negative for each marker individually, as well as for a combined biomarker group, defined as positive if either marker exceeded its respective threshold.

Demographic variables included age, sex, and level of education. Time-related variables comprised the time intervals from injury to blood draw and to CT imaging. Clinical variables included the mechanism of injury (categorized as road traffic injury, fall, or other), initial vital signs, Glasgow Coma Scale (GCS) score upon ED arrival, presence of alcohol intoxication, and concussive symptoms such as loss of consciousness or post-traumatic amnesia. Diagnostic variables included the classification of intracranial injuries and the Injury Severity Score (ISS). Clinical outcomes, including survival and GOS scores, were recorded at hospital discharge and at 1-month and 6-month follow-up.

Statistical analysis

Categorical variables were summarized as counts and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were described as means with standard deviations (SD)

or medians with interquartile ranges (IQRs), and comparisons were made using the t-test or Wilcoxon rank-sum test, depending on data distribution.

To evaluate the diagnostic performance of the biomarkers, sensitivity, specificity, PPV, NPV, LR+, and LR− were calculated. These metrics were derived from 2×2 contingency tables comparing VEUPLEX™ TBI Assay results with the reference standard (CT scan findings). The 95% confidence intervals (CIs) for sensitivity, specificity, PPV, NPV, LR+, and LR− were estimated using the Clopper-Pearson method[18].

To assess the association between serum biomarker levels and long-term clinical outcomes, multivariable logistic regression analysis was conducted to calculate adjusted odds ratios (AORs) with 95% CIs among patients with CT-confirmed intracranial injuries. The model adjusted for potential confounders, including age, sex, time from injury to blood draw, time from injury to CT, mechanism of injury, presence of shock, alcohol intoxication, and initial GCS score.

A sensitivity analysis was conducted in a predefined subgroup meeting the FDA-cleared criteria for serum GFAP and UCH-L1 testing: patients with mild TBI (GCS 13–15) who underwent biomarker testing within 12 h of injury. This subgroup analysis aimed to assess diagnostic performance under conditions consistent with the FDA-approved indication.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Boards of all participating centers: the Institutional Review Board of Seoul National University Hospital (IRB No. SNUH-2103-123-1206), Seoul Metropolitan Government–Seoul National University Boramae Medical Center (IRB No. BMC- 10–2022-47), Seoul National University Bundang Hospital (IRB No. SNUBH-2206-762-402), Chungbuk National University Hospital (IRB No. CBNUH-2022-01-002-001), and Chonnam National University Hospital (IRB No. CHUN-2022-099). Written informed consent was obtained from all participants or, where the participant lacked capacity, from their legally authorized representative. All patient data were anonymized prior to analysis.

Results

Demographic findings and biomarkers

A total of 400 patients with TBI were enrolled between June 21, 2019, and July 31, 2023. Based on head CT findings, 200 patients with intracranial injuries were classified as the CT-positive (CT + TBI) group, while 200 patients without intracranial injuries comprised the CT-negative (CT− TBI) group.

The majority of patients underwent blood sampling (81.5%) and CT imaging (86.3%) within 8 h of injury, with no significant differences observed between the two groups. The ISS was significantly higher in the CT + TBI group compared to the CT− TBI group (median [IQR]: 10 [9–22] vs. 7 [2.5–13], $p < 0.001$). In terms of clinical outcomes, the CT− TBI group demonstrated significantly higher survival rates and more favorable neurological recovery at discharge, 1 month, and 6 months post-injury (all $p < 0.001$) (Table 1).

Median serum concentrations of both GFAP and UCH-L1 were significantly elevated in the CT + TBI group compared to the CT− TBI group (medians [IQR] for GFAP (pg/mL): 129.95 [30.83–823.41] vs. 5.27 [3.48–6.14]; for UCH-L1 (pg/mL): 262.23 [75.88–1170.04] vs. 58.49 [20.91–165.69], both $p < 0.001$) (Table 2 and Fig. 1).

Diagnostic performance of biomarkers

The diagnostic performance of GFAP and UCH-L1 was evaluated using the AUROC for the prediction of CT-confirmed intracranial injuries (Table 3, Fig. 2A). Among the individual biomarkers, GFAP showed superior discrimination, with an AUROC of 0.8900 (95% CI, 0.8568–0.9233), compared to 0.7617 (95% CI, 0.7152–0.8082) for UCH-L1.

Table 4 summarizes the diagnostic metrics of GFAP, UCH-L1, and their combination. The combined biomarker test achieved the highest sensitivity (0.910; 95% CI, 0.870–0.950) and NPV (0.878; 95% CI, 0.825–0.931), outperforming GFAP alone (sensitivity 0.840; NPV 0.845) and UCH-L1 alone (sensitivity 0.715; NPV 0.708). The overall accuracy of the combined test was 0.778 (95% CI, 0.737–0.818), with an OR of 18.37 (95% CI, 10.45–32.30). These findings highlight the complementary diagnostic value of using GFAP and UCH-L1 in combination, particularly for enhancing sensitivity and NPV in the early detection of CT-identifiable intracranial injuries.

Sensitivity analysis

To assess the diagnostic performance of the biomarker assay in a subgroup reflective of the FDA-cleared intended use population, a sensitivity analysis was conducted. Among the 400 enrolled patients, 276 individuals with mild TBI (GCS 13–15) underwent biomarker testing within 12 h of injury. Within this subgroup, 111 patients (40.2%) classified into the CT + TBI group, and 165 patients (59.8%) into the CT− TBI group.

In this subgroup, both biomarkers demonstrated improved diagnostic performance compared to the total study population. The AUROC (95% CI) for GFAP was 0.9023 (0.8651–0.9394), while UCH-L1 showed an AUROC of 0.7735 (0.7189–0.8281), as presented in Table 3 and Fig. 2B. When both biomarkers were used in combination, the assay achieved a sensitivity of 0.973 (95% CI, 0.943–1.000) and a NPV of 0.972 (95% CI, 0.940–1.000), indicating robust discriminatory power for detecting CT-identifiable intracranial injuries in patients with mild TBI (Table 4).

Prognostic performance of biomarkers for long-term clinical outcomes

To evaluate the prognostic utility of serum biomarkers, a multivariable logistic regression analysis was performed among 200 patients with CT-confirmed intracranial injuries (CT + TBI group) (Table 5).

Characteristics	Total	TBI patient		
		CT negative	CT positive	
	N (%)	N (%)	N (%)	P-value
Total	400	200	200	
Demographics				
Age [years], mean (SD)	60.2 (18.2)	56.0 (18.7)	64.5 (16.6)	< 0.001
Male sex	283 (70.8)	140 (70.0)	143 (71.5)	0.742
Time				
Time from injury to blood draw, h				0.582
0 to 8	326 (81.5)	167 (83.5)	159 (79.5)	
8 to 16	26 (6.5)	10 (5.0)	16 (8.0)	
16 to 24	5 (1.3)	3 (1.5)	2 (1.0)	
> 24	43 (10.8)	20 (10.0)	23 (11.5)	
Time from injury to CT examination, h				0.079
0 to 8	345 (86.3)	177 (88.5)	168 (84.0)	
8 to 16	20 (5.0)	10 (5.0)	10 (5.0)	
16 to 24	7 (1.8)	5 (2.5)	2 (1.0)	
> 24	28 (7.0)	8 (4.0)	20 (10.0)	
Injury characteristics				
Mechanism of injury				0.047
Traffic accident	136 (34.0)	69 (34.5)	67 (33.5)	
Fall / Slip down	215 (53.8)	106 (53.0)	109 (54.5)	
Blunt injury	32 (8.0)	21 (10.5)	11 (5.5)	
Others	17 (4.3)	4 (2.0)	13 (6.5)	
Alcohol intake	22 (5.5)	8 (4.0)	14 (7.0)	0.188
Clinical characteristics				
Shock (Initial SBP < 90 mmHg)	38 (9.5)	17 (8.5)	21 (10.5)	0.495
History of loss of consciousness	85 (21.3)	11 (5.5)	74 (37.0)	< 0.001
History of amnesia	17 (4.3)	4 (2.0)	13 (6.5)	0.026
GCS score				< 0.001
3–8	46 (11.5)	3 (1.5)	43 (21.5)	
9–12	25 (6.3)	3 (1.5)	22 (11.0)	
13–15	329 (82.3)	194 (97.0)	135 (67.5)	
Initial GCS, median (IQR)	15 (14–15)	15 (15–15)	15 (10–15)	< 0.001
Injury severity score, median (IQR)	9 (4–17)	7 (2.5–13)	10 (9–22)	< 0.001
Intracranial injury characteristics				
Diffuse axonal injury	15 (3.8)	NA	15 (7.5)	
Intracerebral hemorrhage	38 (9.5)		38 (19.0)	
Subarachnoid hemorrhage	114 (28.5)		114 (57.0)	
Subdural hemorrhage	154 (38.5)		154 (77.0)	
Epidural hemorrhage	40 (10.0)		40 (20.0)	
Intraventricular hemorrhage	20 (5.0)		20 (10.0)	
Clinical outcomes				
Survival to discharge	369 (92.3)	198 (99.0)	171 (85.5)	< 0.001
Favorable neurologic recovery at discharge	341 (85.3)	194 (97.0)	147 (73.5)	< 0.001
Survival at 1 month after injury	353 (88.3)	193 (96.5)	160 (80.0)	< 0.001
Favorable neurologic recovery at 1 month	338 (84.5)	194 (97.0)	144 (72.0)	< 0.001
Survival at 6 months after injury	321 (80.3)	190 (95.0)	131 (65.5)	< 0.001
Favorable neurologic recovery at 6 months	334 (83.5)	195 (97.5)	139 (69.5)	< 0.001

Table 1. Baseline characteristics of the study population: TBI patients with CT-confirmed intracranial injuries and controls. SD, standard deviation; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; IQR, interquartile range.

	Number of patients	Plasma concentration (pg/ml)					
		GFAP			UCH-L1		
		Mean (SD)	Median (IQR)	P-value	Mean (SD)	Median (IQR)	P-value
Total	400	268.40 (576.92)	13.99 (4.89–140.56)		493.19 (817.51)	111.26 (37.54–525.50)	
CT-confirmed				< 0.0001			< 0.0001
CT + TBI group	200	519.59 (731)	129.95 (30.83–823.41)		768.02 (1000.75)	262.23 (75.88–1170.04)	
CT- TBI group	200	14.68 (46.8)	5.27 (3.48–6.14)		215.59 (425.44)	58.49 (20.91–165.69)	

Table 2. Comparison of serum biomarker concentrations between CT-positive and CT-negative TBI groups. SD, standard deviation; IQR, interquartile range; GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-Terminal Hydrolase L1.

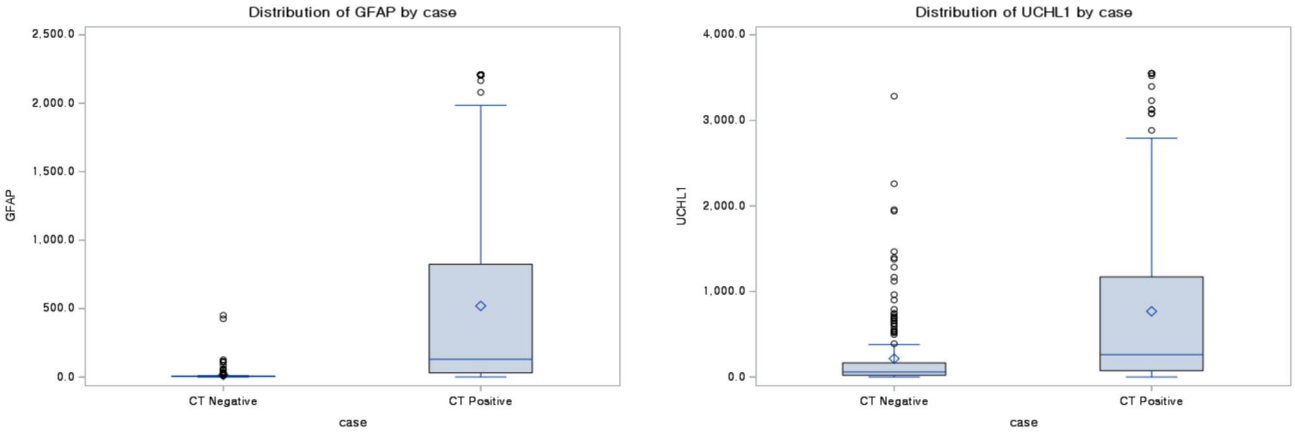


Fig. 1. Distribution of serum GFAP and UCH-L1 concentrations (pg/mL) in CT-positive and CT-negative TBI groups.

	AUROC (95% CI)	P-value
Total population (N = 400)		
UCH-L1	0.7617 (0.7152–0.8082)	< 0.0001
GFAP	0.8900 (0.8568–0.9233)	< 0.0001
Mild TBI with GCS 13–15 (n = 276)		
UCH-L1	0.7735 (0.7189–0.8281)	< 0.0001
GFAP	0.9023 (0.8651–0.9394)	< 0.0001

Table 3. Discriminative performance of UCH-L1 and GFAP for predicting CT-confirmed intracranial injuries. Adjusted for sex and age. GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-Terminal Hydrolase L1; AUROC, Area Under the Receiver Operating Characteristic Curve; CI, confidence interval.

The combined biomarker assay was significantly associated with reduced 6-month survival (AOR [95% CI]: 0.09 [0.01–0.84]). However, while the combined assay did not show a statistically significant association with favorable neurological outcomes at 6 months (AOR [95% CI]: 0.45 [0.07–2.88]), elevated UCH-L1 levels alone were significantly associated with decreased odds of favorable neurological recovery (AOR [95% CI]: 0.17 [0.05–0.62]).

Although 1-month outcomes were also available, the number of events was limited, leading to imprecise estimates (Table S2). Therefore, we focused on 6-month outcomes, which are more widely used as a clinically meaningful endpoint in TBI research.

Discussion

This study demonstrated that rapid, simultaneous quantification of GFAP and UCH-L1 using a POCT platform enables effective identification of CT-identifiable intracranial injuries in a real-world ED setting. Among 400 TBI patients with and without intracranial injuries, the combined biomarker assay showed good diagnostic performance, with a sensitivity of 91.0% and a NPV of 87.8%. This capability may allow for earlier detection of subtle but clinically significant injuries, enabling more precise and physiologically informed decision-making in acute TBI care.

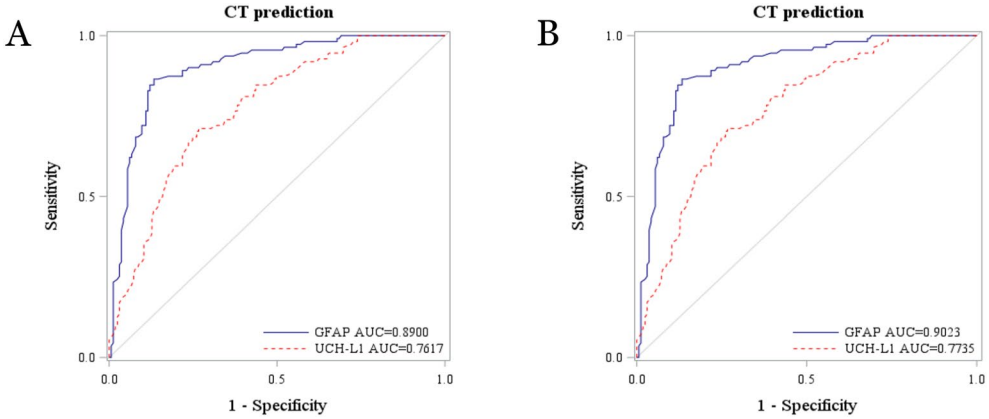


Fig. 2. Receiver operating characteristic (AUROC) curves for GFAP and UCH-L1 in predicting CT-confirmed intracranial injuries: (**A**) Total study population, (**B**) Subgroup of mild TBI patients tested within 12 h of injury.

	Sensitivity	Specificity	PPV	NPV	LRP	LRN	Accuracy	OR
Total								
GFAP	0.840 (0.789–0.891)	0.870 (0.823–0.917)	0.866 (0.818–0.914)	0.845 (0.795–0.894)	6.462 (7.516–5.555)	0.184 (0.213–0.159)	0.855 (0.821–0.890)	35.14 (20.09–61.46)
UCH-L1	0.715 (0.652–0.778)	0.690 (0.626–0.754)	0.698 (0.635–0.760)	0.708 (0.644–0.772)	2.306 (2.717–1.958)	0.413 (0.488–0.350)	0.703 (0.658–0.747)	5.58 (3.64–8.58)
Combined	0.910 (0.870–0.950)	0.645 (0.579–0.711)	0.719 (0.664–0.775)	0.878 (0.825–0.931)	2.563 (2.964–2.217)	0.140 (0.166–0.117)	0.778 (0.737–0.818)	18.37 (10.45–32.30)
Mild TBI with GCS 13–15 (n = 276)								
GFAP	0.865 (0.801–0.929)	0.867 (0.815–0.919)	0.814 (0.743–0.884)	0.905 (0.859–0.951)	6.486 (7.684–5.476)	0.156 (0.190–0.128)	0.866 (0.826–0.906)	41.60 (20.55–84.23)
UCH-L1	0.748 (0.667–0.829)	0.673 (0.601–0.744)	0.606 (0.524–0.688)	0.799 (0.732–0.865)	2.285 (2.755–1.895)	0.375 (0.465–0.303)	0.703 (0.649–0.757)	5.58 (3.64–8.58)
Combined	0.973 (0.943–1.000)	0.624 (0.550–0.698)	0.635 (0.563–0.708)	0.972 (0.940–1.000)	2.589 (3.026–2.216)	0.043 (0.054–0.035)	0.765 (0.714–0.815)	59.80 (18.20–196.49)

Table 4. Diagnostic performance of UCH-L1, GFAP, and the combined assay in detecting CT-confirmed intracranial injuries. GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-Terminal Hydrolase L1; TBI, traumatic brain injury; CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value; LRP, likelihood ratio positive; LRN, likelihood ration negative; OR, odds ratio.

Importantly, this study extended the utility of biomarker testing beyond early diagnosis by evaluating long-term clinical outcomes. Patients with UCH-L1 levels above the predefined cutoff had a significantly lower 6-month survival (AOR [95% CI]: 0.34 [0.13–0.90]) and were less likely to achieve favorable neurological recovery (AOR [95% CI]: 0.17 [0.05–0.62]). For the combined biomarker assay, the AOR for 6-month mortality was even lower (AOR [95% CI]: 0.09 [0.01–0.84]). Our findings are consistent with those from the TRACK-TBI study, which demonstrated that day-of-injury GFAP and UCH-L1 concentrations have good to excellent prognostic performance for predicting 6-month mortality and unfavorable outcomes[4]. These results suggest that bedside POCT measurement of GFAP and UCH-L1 not only enhances early detection of intracranial injury but may also be associated with long-term outcomes following TBI.

However, these estimates should be interpreted with caution, as the number of outcome events within subgroups was limited, resulting in relatively wide confidence intervals and potential imprecision in effect size estimation. Therefore, while the observed associations support the potential prognostic relevance of early biomarker elevation, further studies with larger sample sizes are needed to validate these findings.

Cellular and molecular basis for differential performance of GFAP and UCH-L1

GFAP is an intermediate filament protein found almost exclusively in astrocytes. It is released into the bloodstream when astroglial cells are damaged or when the blood–brain barrier is disrupted[19]. Given its central nervous system specificity and a circulating half-life of approximately 24–72 h, GFAP is particularly valuable for detecting focal injuries, such as hemorrhagic lesions identifiable on CT scans[20].

In contrast, UCH-L1 is a neuron-specific deubiquitinating enzyme that plays a key role in protein homeostasis via the ubiquitin–proteasome system[21]. It is abundantly expressed in neuronal cytoplasm and released into peripheral blood following neuronal cell injury, including axonal damage or diffuse brain injury. Because of its neuronal specificity and stability, UCH-L1 serves as a reliable marker of diffuse neuronal damage and has

Outcomes	Outcome, n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
6-month survival			
Serum GFAP level			
< 17 pg/mL	28/32 (87.5)	Reference	Reference
≥ 17 pg/mL	103/168 (61.3)	0.23 (0.08–0.68)	0.31 (0.09–1.12)
Serum UCH–L1 level			
< 101 pg/mL	46/57 (80.7)	Reference	Reference
≥ 101 pg/mL	85/143 (59.4)	0.35 (0.17–0.73)	0.34 (0.13–0.90)
Serum GFAP or UCH–L1 level			
both below cutoff	17/18 (94.4)	Reference	Reference
either above cutoff	114/182 (62.6)	0.10 (0.01–0.76)	0.09 (0.01–0.84)
Favorable GOS score at 6-month			
Serum GFAP level			
< 17 pg/mL	28/32 (87.5)	Reference	Reference
≥ 17 pg/mL	111/168 (66.1)	0.28 (0.09–0.83)	0.38 (0.09–1.73)
Serum UCH–L1 level			
< 101 pg/mL	49/57 (86.0)	Reference	Reference
≥ 101 pg/mL	90/143 (62.9)	0.28 (0.12–0.63)	0.17 (0.05–0.62)
Serum GFAP or UCH–L1 level			
both below cutoff	15/18 (83.3)	Reference	Reference
either above cutoff	124/182 (68.1)	0.43 (0.12–1.54)	0.45 (0.07–2.88)

Table 5. Multivariable logistic regression analysis of serum biomarkers for predicting 6-month clinical outcomes among 200 patients with CT-confirmed intracranial injuries. Adjusted for demographics (age, sex), time variables (time from injury to blood draw, time from injury to CT examination) injury mechanism, shock, alcohol intake, and Glasgow Coma Scale . GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-Terminal Hydrolase L1; OR, odds ratio; CI, confidence interval.

shown stronger associations with long-term neurological outcomes, even when initial neuroimaging appears unremarkable[22,23]. In our study, UCH-L1 positivity was independently associated with a significantly reduced likelihood of favorable neurological recovery, supporting its potential role in identifying injuries that are not visible on CT but are critical determinants of prognosis[24,25].

These molecular characteristics likely explain the distinct performance patterns observed in this study. GFAP demonstrated higher diagnostic accuracy for CT-identifiable intracranial injuries, reflecting its sensitivity to focal astrocytic injury[26,27]. UCH-L1 showed a stronger association with long-term functional outcomes, consistent with its ability to detect diffuse or microscopic neuronal damage that may not be captured on CT[23]. These complementary release profiles are consistent with detailed reviews of the structure, function, and post-injury kinetics of the two proteins, which emphasise that GFAP and UCH-L1 are most informative when interpreted as a tandem pair reflecting distinct compartments of brain injury — astroglial and neuronal — rather than as interchangeable markers of a single process[14].

Significance and context

These findings should be interpreted in the context of prior large-scale and regulatory studies, particularly ALERT-TBI and subsequent POCT-based investigations. Previous studies have primarily investigated the utility of serum biomarkers such as GFAP and UCH-L1 for detecting acute intracranial abnormalities on head CT, particularly in patients with mild TBI[13,26,28]. However, data on the association between early biomarker levels and long-term clinical outcomes remain limited. For instance, the TRACK-TBI study demonstrated an association between GFAP and 6-month functional impairment in mild TBI patients, but its prognostic utility in more severe cases or real-world ED settings was unclear[26].

In our study, a sensitivity analysis limited to patients with mild TBI (GCS 13–15) tested within 12 h of injury—in line with the FDA-cleared indication—showed improved diagnostic performance (sensitivity: 97.3%, NPV: 97.2%). These values are comparable to those reported in the FDA clearance study (sensitivity: 97.6%, NPV: 99.6%)[13]. Notably, the cutoff values used in the present study (GFAP: 17 pg/mL; UCH-L1: 101 pg/mL) were lower than those reported in prior studies and FDA-cleared platforms, including the ALERT-TBI study (22 pg/mL and 327 pg/mL, respectively) and rapid cartridge-based assays such as Abbott i-STAT (approximately 30–35 pg/mL for GFAP and 360–400 pg/mL for UCH-L1).

These differences are likely attributable to variations in analytical performance characteristics across platforms. The VEUPLEX™ TBI assay demonstrated lower limits of detection and quantification compared with previously approved assays, enabling more sensitive detection of low-level biomarker elevations (Table 6). Consequently, the distribution of measured biomarker concentrations may shift toward lower ranges, necessitating lower cutoff values to achieve optimal diagnostic performance. The translational trajectory of this biomarker pair — from initial discovery, through the first FDA clearance in 2018, to point-of-care and core-laboratory formats such as

	Company (product)	LOD	LLOQ	ULOQ	Cutoff (pg/mL)
GFAP	VEUPLEX™ TBI Assay	0.384	3.1	400	17
	Banyan (DEN170045[10]	N/A	9	321	22
	Abbott (K201778)[12]	23	30	10,000	30
	Abbott (K223602)[29]	3.2	6.1	42,000	35
UCH-L1	VEUPLEX™ TBI Assay	0.788	6.25	800	101
	Banyan (DEN170045)[10]	N/A	79	2,561	327
	Abbott (K201778)[12]	70	200	3,200	360
	Abbott (K223602)[29]	18.3	26.3	25,000	400

Table 6. Analytical performance characteristics and cutoff values of GFAP and UCH-L1 across different diagnostic platforms. Values represent the analytical performance characteristics of representative GFAP and UCH-L1 assay platforms, including limit of detection (LOD), lower limit of quantification (LLOQ), upper limit of quantification (ULOQ), and diagnostic cutoff values. Data for FDA-cleared devices were obtained from publicly available regulatory documents and manufacturer reports. GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1; LOD, limit of detection; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification.

the i-STAT Alinity and the CE-marked VIDAS TBI assay — has been reviewed in detail elsewhere, and illustrates that assay-specific analytical characteristics, sample matrix (serum versus plasma), and the intended clinical use of each platform have consistently driven platform-specific threshold selection[15]. This reinforces our view that the lower thresholds derived here should be interpreted in relation to the analytical characteristics of the VEUPLEX™ assay rather than compared directly with values reported for other technologies.

Importantly, the cutoff values in this study were derived using ROC-based analysis with a predefined emphasis on high sensitivity, consistent with the intended clinical role of the assay as a rule-out tool. This approach differs from prior studies that primarily adopted regulatory or platform-specific thresholds, which may reflect different performance priorities.

Taken together, these findings suggest that cutoff values are inherently platform-dependent and should be interpreted within the context of assay-specific analytical characteristics and intended clinical use, rather than being directly compared across different technologies.

Clinical implications

In Korea, more than 100,000 people present to EDs annually for TBI, with approximately 4,000 TBI-related deaths each year[30]. Early risk identification enables timely decisions on intensive monitoring, specialist referral, ICU admission, and rehabilitation. This study extends prior findings by highlighting the prognostic value of biomarkers in predicting long-term outcomes, supporting more personalized care and efficient resource use in TBI management.

The combined use of glial (GFAP) and neuronal (UCH-L1) biomarkers offers a more comprehensive assessment of injury patterns in TBI and enables more effective early risk stratification[22]. The assay showed high sensitivity and NPV, particularly in patients with mild TBI tested within 12 h, supporting its potential to reduce unnecessary CT scans and inform timely clinical decisions. These findings are consistent with previous studies demonstrating that GFAP exhibits high sensitivity and negative predictive value even at very early time points after injury, supporting its role as a rule-out tool for safely reducing unnecessary CT imaging[31]. In resource-limited or high-volume settings, rapid biomarker testing could enhance triage, expedite treatment, and streamline emergency care workflows[32].

However, despite these advantages, the relatively modest specificity of the combined GFAP/UCH-L1 assay warrants careful interpretation. The assay demonstrated high sensitivity and negative predictive value, particularly in the mild TBI subgroup; however, its relatively modest specificity suggests that it is best positioned as a rule-out tool rather than a stand-alone rule-in test.

In clinical practice, high sensitivity is essential to minimize the risk of missed intracranial injury, supporting the safe reduction of CT imaging in selected low- to intermediate-risk patients. A negative biomarker result, particularly when used in conjunction with established clinical decision rules, may help identify patients who can be safely discharged without imaging.

However, the lower specificity may result in false-positive findings, potentially leading to over-triage, increased observation, or CT imaging that may ultimately prove unnecessary. Therefore, biomarker results should be interpreted within the broader clinical context rather than used in isolation.

An important clinical implication of these findings is the potential integration of biomarker testing with existing clinical decision rules, rather than replacing them. Established rules such as the Canadian CT Head Rule and the New Orleans Criteria are widely used to guide CT utilization in patients with TBI; however, they rely solely on clinical variables and may still result in unnecessary imaging or residual uncertainty in low-risk patients.

The addition of a rapid biomarker assay, such as the VEUPLEX™ platform, provides an objective biological measure of brain injury that can complement clinical assessment. In patients classified as low- to intermediate-risk by clinical decision rules, a negative biomarker result could further reduce the probability of clinically significant intracranial injury, potentially allowing for safer discharge without CT imaging. Conversely,

in settings with limited imaging resources, biomarker testing may help prioritize patients at higher risk for intracranial pathology, thereby improving resource allocation.

Taken together, this combined approach may enhance both safety and efficiency by reducing unnecessary CT scans while minimizing the risk of missed intracranial injury.

Importantly, the interpretation of predictive values should take into account differences in disease prevalence between the study population and real-world clinical settings. Although the 1:1 case–control design in this study resulted in an artificially elevated CT-positive prevalence (50%), this approach allowed balanced evaluation of diagnostic performance. In contrast, real-world prevalence is substantially lower, with prior FDA-cleared studies reporting approximately 6.3% and population-based data in Korea suggesting a prevalence of 8.6%[33].

To address this, we estimated predictive values across a range of plausible prevalence scenarios using FDA-recommended equations (Table S3 and Figure S2). As expected, PPV increased and NPV decreased with increasing prevalence. Under the high-prevalence condition of this study, the lower bound of the 95% confidence interval for NPV was lower than that of the comparator device (Abbott i-STAT, 92.4%). However, when applying more clinically relevant prevalence estimates (6.3–8.6%), the VEUPLEX™ TBI assay is expected to yield higher NPV values and corresponding confidence interval bounds than those observed in this study.

These findings suggest that, under real-world conditions, the assay may demonstrate equal or improved rule-out performance compared with existing devices, supporting its clinical utility in safely reducing unnecessary CT imaging.

Taken together, this combined approach may enhance both safety and efficiency by reducing unnecessary CT scans while minimizing the risk of missed intracranial injury.

Limitations

Several limitations of this study should be acknowledged. First, the analysis was limited to two biomarkers—GFAP and UCH-L1. While these provide valuable insights into astroglial and neuronal injury, TBI involves a complex interplay of molecular mechanisms. Including additional biomarkers that reflect other aspects of TBI pathophysiology—such as axonal injury, neuroinflammation, or synaptic dysfunction—may improve both diagnostic and prognostic accuracy. Future studies should explore broader biomarker panels to provide a more comprehensive understanding of injury burden and recovery trajectory. Furthermore, functional outcomes were assessed using the Glasgow Outcome Scale (GOS), whereas the Glasgow Outcome Scale–Extended (GOSE), which allows for more detailed and sensitive evaluation of long-term neurological outcomes, was not collected in this study.

Second, potential confounding effects from extracranial injuries—such as abdominal, thoracic, or orthopedic trauma—were not explicitly considered. These injuries can induce systemic inflammatory responses or release proteins that may affect serum biomarker levels, potentially limiting the brain specificity of GFAP and UCH-L1. Future research should consider including isolated TBI controls or adding markers specific to extracranial injury to reduce this potential confounding.

Third, biomarker levels were assessed only once, within 24 h of injury. While early sampling supports rapid triage, it may not fully capture the temporal kinetics of biomarker release. GFAP typically peaks early and declines, while UCH-L1 may remain elevated longer in cases of ongoing neuronal damage[24,26]. These dynamics may explain the differential diagnostic and prognostic performance observed. In addition, the cutoff values applied in this study were based on predefined analytical thresholds intended for diagnostic use and were not specifically optimized for prognostic purposes. Data-driven approaches to identify outcome-specific cutoff values, such as ROC-based optimization, were not performed. Future studies should explore whether alternative thresholds may improve prognostic accuracy.

Finally, although we adhered to STARD 2015 reporting guidelines, some aspects of model evaluation were limited as this study was not designed as a formal prediction model development study.

Conclusions

This study demonstrates that rapid measurement of GFAP and UCH-L1 using a POCT platform can accurately identify CT-identifiable intracranial injuries and provide valuable prognostic information regarding 6-month survival and functional outcomes. These findings support the clinical utility of these biomarkers for both acute diagnostic evaluation and long-term risk stratification in patients with TBI. Given the distinct diagnostic and prognostic profiles of GFAP and UCH-L1, future research should investigate broader biomarker panels and longitudinal sampling strategies to further enhance the precision and impact of TBI management.

Data availability

The data for the study were obtained from the Korea Medical Device Development Fund, but restrictions apply to the availability of these data and so are not publicly available, but are available from the corresponding author on reasonable request.

Code availability

No custom code, algorithm, or software pipeline was developed for this study. All analyses were performed using commercially available statistical software (SAS version 9.4; SAS Institute Inc., Cary, NC, USA) and publicly available, previously published R packages. No bespoke code is therefore available for deposition.

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References

1. Peeters, W. et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir. (Wien)***157**(10), 1683–1696 (2015).
2. Injury GBDTB, Spinal Cord Injury C. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**(1):56–87. (2019).
3. Cortes, D. & Pera, M. F. The genetic basis of inter-individual variation in recovery from traumatic brain injury. *NPJ Regen Med.***6**(1), 5 (2021).
4. Korley, F. K. et al. Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: an observational cohort study. *Lancet Neurol.***21**(9), 803–813 (2022).
5. Morton, M. J. & Korley, F. K. Head computed tomography use in the emergency department for mild traumatic brain injury: integrating evidence into practice for the resident physician. *Ann. Emerg. Med.***60**(3), 361–367 (2012).
6. Brenner, D. J. & Hall, E. J. Computed tomography—an increasing source of radiation exposure. *N. Engl. J. Med.***357**(22), 2277–2284 (2007).
7. Sharp, A. L. et al. Computed tomography use for adults with head injury: Describing likely avoidable emergency department imaging based on the Canadian CT head rule. *Acad. Emerg. Med.***24**(1), 22–30 (2017).
8. Stein, S. C., Burnett, M. G. & Glick, H. A. Indications for CT scanning in mild traumatic brain injury: A cost-effectiveness study. *J. Trauma***61**(3), 558–566 (2006).
9. Schellenberg, M., Benjamin, E., Owattanapanich, N., Inaba, K. & Demetriades, D. The impact of delayed time to first CT head in traumatic brain injury. *Eur. J. Trauma Emerg. Surg.***47**(5), 1511–1516 (2021).
10. Huibregtse, M. E., Bazarian, J. J., Shultz, S. R. & Kawata, K. The biological significance and clinical utility of emerging blood biomarkers for traumatic brain injury. *Neurosci. Biobehav. Rev.***130**, 433–447 (2021).
11. Welch, R. D. et al. Ability of serum glial fibrillary acidic protein, ubiquitin C-terminal hydrolase-L1, and S100B to differentiate normal and abnormal head computed tomography findings in patients with suspected mild or moderate traumatic brain injury. *J. Neurotrauma***33**(2), 203–214 (2016).
12. Bazarian, J. J. et al. Accuracy of a rapid glial fibrillary acidic protein/ubiquitin carboxyl-terminal hydrolase L1 test for the prediction of intracranial injuries on head computed tomography after mild traumatic brain injury. *Acad. Emerg. Med.***28**(11), 1308–1317 (2021).
13. Bazarian, J. J. et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): A multicentre observational study. *Lancet Neurol.***17**(9), 782–789 (2018).
14. Wang, K. K. W., Kobeissy, F. H., Shakkour, Z. & Tyndall, J. A. Thorough overview of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein as tandem biomarkers recently cleared by US Food and Drug Administration for the evaluation of intracranial injuries among patients with traumatic brain injury. *Acute Med. Surg.***8**(1), e622 (2021).
15. Kobeissy, F. et al. The game changer: UCH-L1 and GFAP-based blood test as the first marketed in vitro diagnostic test for mild traumatic brain injury. *Expert Rev. Mol. Diagn.***24**(1–2), 67–77 (2024).
16. Bossuyt, P. M. et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. *BMJ***351**, h5527 (2015).
17. Kim, M. et al. Length-encoded rod-shaped magnetic particle-based multipurpose immuno- and molecular assay system for rapid and accurate diagnostics: VEUS. *Chem. Eng. J.***509**, 161118 (2025).
18. Clopper, C. J. & Pearson, E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika***26**(4), 404–413 (1934).
19. Verboon, L. N., Patel, H. C. & Greenhalgh, A. D. The immune system's role in the consequences of mild traumatic brain injury (concussion). *Front. Immunol.***12**, 620698 (2021).
20. Papa, L. et al. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Ann. Emerg. Med.***59**(6), 471–483 (2012).
21. Mondello, S. et al. Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: A case control study. *Crit. Care***15**(3), R156 (2011).
22. Mondello, S. et al. Glial neuronal ratio: A novel index for differentiating injury type in patients with severe traumatic brain injury. *J. Neurotrauma***29**(6), 1096–1104 (2012).
23. Whitehouse, D. P. et al. Relationship of admission blood proteomic biomarkers levels to lesion type and lesion burden in traumatic brain injury: A CENTER-TBI study. *EBioMedicine***75**, 103777 (2022).
24. Helmrich, I. et al. Incremental prognostic value of acute serum biomarkers for functional outcome after traumatic brain injury (CENTER-TBI): An observational cohort study. *Lancet Neurol.***21**(9), 792–802 (2022).
25. Mondello, S. et al. Clinical utility of serum levels of ubiquitin C-terminal hydrolase as a biomarker for severe traumatic brain injury. *Neurosurgery***70**(3), 666–675 (2012).
26. Yue, J. K. et al. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. *Lancet Neurol.***18**(10), 953–961 (2019).
27. Abdelhak, A. et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. *Nat. Rev. Neurol.***18**(3), 158–172 (2022).
28. Karamian, A. et al. Accuracy of GFAP and UCH-L1 in predicting brain abnormalities on CT scans after mild traumatic brain injury: A systematic review and meta-analysis. *Eur. J. Trauma Emerg. Surg.***51**(1), 68 (2025).
29. Welch, R. D. et al. A high-performance core laboratory GFAP/UCH-L1 test for the prediction of intracranial injury after mild traumatic brain injury. *Am. J. Emerg. Med.***89**, 129–134 (2025).
30. Kong, S. Y., Ro, Y. S., Shin, S. D., Song, K. J. & Park, J. H. Epidemiology of traumatic brain injury in the Republic of Korea from 2011 to 2014: Based on three major data sources in the Republic of Korea. *J. EMS Med.***1**(1), 13–22 (2011).
31. Papa, L. et al. Diagnostic performance of GFAP, UCH-L1, and MAP-2 within 30 and 60 minutes of traumatic brain injury. *JAMA Netw. Open***7**(9), e2431115 (2024).
32. Mondello, S. et al. Serum concentrations of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein after pediatric traumatic brain injury. *Sci. Rep.***6**(1), 28203 (2016).
33. Park, S. Y., Jung, J. Y., Kwak, Y. H., Kim, D. K. & Suh, D. B. A Nationwide Study on the Epidemiology of Head Trauma and the Utilization of Computed Tomography in Korea. *J. Trauma Injury.***25**(4), 152–158 (2012).

Author contributions

YSR and HY had full access to all of the data in the study and take responsibility for the integrity of the data as well as the accuracy of the data analysis. Conceptualization: HY and YSR Data curation: HY, JJ, EJ, and GJP Formal analysis: HY Funding acquisition: YSR, YGJ, and SHS Investigation: YSR, HY, JJ, EJ, and GJP Methodology: HY, YSR, and SDS Software: HY Supervision: YSR, BMO, SHS, and SDS Validation: JJ, EJ, and GJP Writing—original draft: HY Writing—review & editing: YSR, YGJ, BMO, SHS, and SDS Approval of final manuscript: all authors.

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Declarations

Competing interests
The authors declare no competing interests.

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