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ORIGINAL ARTICLE

Evaluation of brain injury biomarkers in mild traumatic brain injury with and without computed tomography findings

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ABSTRACT

Aim Mild traumatic brain injury (mTBI) presents diagnostic challenges, with head computed tomography (head CT) often overutilized in emergency settings. Blood biomarkers such as glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) have shown promise in early injury detection. The aim of this study was to evaluate the diagnostic utility of GFAP and UCH-L1 in identifying intracranial injuries early and potential reduction in unnecessary head CT scans in mTBI patients.
Methods A prospective study was conducted on 102 adult patients with mTBI. Serum levels of GFAP and UCH-L1 were measured within 12 hours after injury and compared with head CT findings using appropriate statistical analyses.
Results Both biomarkers demonstrated 100% sensitivity and moderate specificity, with high negative predictive value (NPV), supporting their utility in ruling out injuries detectable on CT.
Conclusion GFAP and UCH-L1 are effective early biomarkers for excluding significant intracranial injuries and may help optimize head CT scan utilization in the acute management of mTBI.
Key words: GFAP, neurotrauma, UCH-L1

INTRODUCTION

Mild traumatic brain injury **(**mTBI) is a prevalent public health concern due to its high incidence, acute effects, and potential long-term cognitive and functional consequences (1). Head CT remains the standard imaging modality used for the initial assessment of patients with suspected TBI in emergency departments (2). However, growing evidence suggests that head CT is frequently overused in mild cases, often yielding negative findings, which leads to unnecessary radiation exposure and increased healthcare costs (3). Furthermore, the diagnostic and prognostic accuracy of standard clinical tools, such as the Glasgow Coma Scale (GCS), is limited by external factors including intoxication, comorbidities, advanced age, or the presence of other injuries (4).

While neuroimaging can visualize structural brain damage and guide surgical decisions, it provides limited information about a patient's long-term functional prognosis, particularly in cases of mild or moderate injury (5). Studies have shown that a substantial proportion of mTBI patients present with no head CT abnormalities despite exhibiting neurological symptoms, further highlighting the need for complementary diagnostic tools. To address these limitations, research has increasingly focused on fluid-based biomarkers that are released into the systemic circulation following injury to brain tissue (6). Among these, glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) have emerged as promising neuron-specific biomarkers with demonstrated diagnostic utility in mTBI (7). GFAP is an intermediate filament protein expressed predominantly in astrocytes, where it plays a role in synaptic regulation, inflammatory responses, and axonal regeneration (8). Its serum concentration increases as a consequence of astrocytic damage, peaking around 20 hours after trauma, and remaining elevated for up to 7 days. The optimal time window for GFAP sampling is considered to be between 6 and 18 hours post-injury. UCH-L1 is a neuron-specific protease involved in the degradation of ubiquitinated proteins. It is highly abundant in neurons and constitutes approximately 5% of total brain protein (6). Upon injury, UCH-L1 level rises rapidly, peaking within 8 hours and returning to baseline shortly thereafter. The biomarker is most effective in the early stages of trauma, with an optimal sampling window between 2 and 8 hours (5). Both biomarkers are minimally expressed in non-neuronal tissues, contributing to their high specificity for central nervous system injury (6).

Numerous studies have evaluated the utility of GFAP and UCH-L1 in the detection of intracranial injury following

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mTBI. Some of them have demonstrated that the combined use of these biomarkers, interpreted against predefined thresholds, yields high negative predictive value (NPV) in ruling out CT-detectable lesions in mTBI patients (9,10). Additionally, these biomarkers are being investigated for their prognostic potential in predicting long-term neurological outcomes (11).
Although blood biomarkers including GFAP and UCH-L1 offer a promising adjunct to identify patients at risk of intracranial injury, validated clinical guidelines still rely mainly on head CT, and biomarker-guided strategies are not yet widely implemented in everyday practice (12) . Recent multicentre data using a rapid point of care assay suggest that GFAP and UCH-L1 testing can support decision-making on head CT indication and may offer a cost and time effective approach to the management of patients with mTBI in emergency settings (13). Further support for the use of GFAP and UCH-L1 as a rule out tool to safely reduce head CT utilization in mTBI comes from a recent European multicentre study, which showed that combined testing of these biomarkers can reliably exclude intracranial lesions while decreasing unnecessary CT scans (14).
This single-centre study evaluated GFAP and UCH-L1 as rapid blood biomarkers for the early exclusion of intracranial injury in patients with suspected mTBI within 12 hours of trauma, with a particular focus on their practical clinical use beyond multicentre or laboratory-based trials. The aim was to determine their diagnostic accuracy (sensitivity, specificity and negative predictive value) and to assess whether they can safely reduce reliance on head CT.

PATIENTS AND METHODS

Patients and study design

This prospective observational study was conducted at the University Clinical Centre (UCC) Tuzla over an eight-month period (August 2024-March 2025). A total of 102 adult patients (≥18 years) with mTBI were included. mTBI was defined based on a Glasgow Coma Scale (GCS) score of 13 -15 on admission (15) in accordance with internationally accepted criteria (16).
The study protocol was reviewed and approved by the Ethics Committee of UCC Tuzla (Approval No. 02-09/2-114/23) and a written informed consent was obtained from all participants prior to inclusion.
Inclusion criteria were: age ≥18 years, hospital admission within 12 hours post-injury, GCS 13–15, and availability of both serum biomarker tests (GFAP and UCH-L1) and head CT imaging. Exclusion criteria included GCS <13, penetrating head trauma, polytrauma, current treatment with anticoagulants, venous blood sampling conducted more than 12 hours after injury, preexisting neurological diseases and severe intoxication interfering with neurological assessment. The diagnosis of mTBI was based on accepted clinical criteria, including GCS 13–15, loss of consciousness <30 minutes, and post-traumatic amnesia <24 hours (16). A CT-positive finding was defined as the presence of intracranial haemorrhage (subarachnoid, subdural, epidural, or intracerebral), cerebral contusions, or skull fractures. Patients without acute intracranial findings were classified as CT-negative.

Methods

Venous blood samples were collected upon hospital admission and in all cases within 12 hours of the traumatic event. Blood was drawn into 6 mL serum tubes with clot activator (Vacusera CAT Serum, Disera A.Ş., İzmir, Turkey) and immediately transported to the Department of Biochemistry at the UCC Tuzla Polyclinic for Laboratory Diagnostics for processing. In the laboratory, samples were allowed to clot for approximately 30 minutes at room temperature (total time from venipuncture to centrifugation ≈30 minutes), followed by centrifugation at 3000 rpm for 7 minutes (≈21 000 g-minutes) in accordance with the manufacturer's instructions for the Alinity assay (Abbott, USA), to ensure complete separation of serum and removal of cellular components (17). Prior to analysis, all serum samples were visually inspected for haemolysis, lipemia, and icterus. Samples exhibiting visible discoloration or turbidity were excluded from testing to avoid analytical interference. The haemolysis, icterus and lipemia (HIL) index detection module was not enabled on the Alinity i analyser, therefore visual inspection served as the preanalytical quality-control step. All biomarker analyses were performed within two hours after centrifugation.
Serum concentrations GFAP and UCH-L1 were quantified using chemiluminescent microparticle immunoassay (CMIA) technology on the Alinity i analyser (Alinity i TBI assay, Abbott, USA). Diagnostic cut-off values were 35 pg/mL for GFAP and 400 pg/mL for UCH-L1, as recommended in the Alinity i TBI assay documentation. Samples exceeding either threshold were interpreted as positive. According to the manufacturer's algorithm, the overall TBI test result was considered positive if either biomarker exceeded its respective threshold (17).

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables with normal distribution, and as median with interquartile range (Q1–Q3) for non-normally distributed variables. Categorical data were presented as frequencies and percentages. Differences in the distribution of categorical variables were assessed using Pearson's $\chi 2$ test. Comparisons of continuous variables between two independent groups were performed using the Mann–Whitney U test. Correlations between continuous variables (age, GCS, GFAP, UCH-L1, and time from injury to blood draw) were evaluated using Spearman's rank correlation coefficient (rho). Diagnostic performance of GFAP and UCH-L1 was assessed using receiver operating characteristic (ROC) curve analysis. For predefined decision thresholds, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated from 2×2 contingency tables using head CT findings as the reference standard. A $p< 0.05$ was considered statistically significant.

RESULTS

A total of 102 patients were enrolled in the study, comprising 76 (75%) males and 26 (25%) females ($p<0.001$), yielding a male-to-female ratio of 2.92. The median age of participants was 49.5 years, with an interquartile range (IQR) of 32.0 to 63.0 years. The youngest patient was 18 years old, the oldest was 87. All patients presented with GCS between 13 and 15 (median 15; IQR: 14–15). Ninety-nine (of 102) patients had blood drawn within 6 hours of injury, and three were sampled after 6 hours. Overall median time from injury to blood draw was 3.0 hours (IQR 2.0–4.0) (Table 1). No statistically significant sex differences were found in any of the continuous variables analysed, including GCS scores, GFAP, and UCH-L1

Table 1. Characteristics of the continuous parameters of the age, GCS, GFAP, UCH-L1 and time from injury to sampling for the entire study population (N=102)

Parameters	Mean (SD)	Min. – Max.	Median	IQR (25%-75%)	
Age (years)	47.77 (18.845)	18-87	49.50	32.00	63.0
GCS	14.60 (0.601)	13-15	15.00	14.00	15.0
GFAP (pg/mL)	1160.14 (4010.33)	8.4-26014.4	114.45	26.27	515.85
UCH-L1 (pg/mL)	2112.90 (3610.94)	112.7-28830.3	797.75	361.0	2168.05
Time* (hours)	3.4412 (1.40419)	2.00-9.00	3.00	2.00	4.00

Time*, interval from injury to blood sampling (hours);
SD, standard deviation; Min.-Max, minimum-maximum; IQR, interquartile range; GSC, Glasgow Coma Scale; GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-terminal Hydrolase L1.

concentrations (p>0.05 for all comparisons). The age showed a positive correlation with GFAP and UCH-L1, but a negative correlation with GSC, GSC was negatively correlated with GFAP, UCH-L1 and time from blood draw; GFAP exhibited a positive correlation with UCH-L1 (Table 2).

Among 102 patients, 58 (57%) had injuries caused by traffic accidents, 31 (30%) were caused by falling, and 13 (13%) had injuries from other causes (fights, occupational) (p<0.001).

Out of a total of 102 patients, 35 (34%) had CT-confirmed mTBI, 67 (66%) had no detectable abnormalities on CT imaging (p=0.002).

Table 2. Correlation between continuous parameters: age, GCS, GFAP, UCH-L1 and time from injury to sampling (N=102)

Parameters		Age (years)	GSC	GFAP (pg/mL)	UCH-L1 (pg/mL)
GSC	rho	-0.474			
	p	<.001			
GFAP (pg/mL)	rho	0.505	-0.679		
	p	<.001	<.001		
UCH-L1 (pg/mL)	rho	0.255	-0.362	0.501	
	p	<.001	<.001	<.001	
Time* (h)	rho	0.107	-0.233	0.159	0.047
	p	0.283	0.018	0.112	0.636

Time*, interval from injury to blood sampling (hours);
GSC, Glasgow Coma Scale; GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-terminal Hydrolase L1.

Biomarker analysis revealed that 80 (78%) patients tested positive for mTBI based on GFAP and/or UCH-L1 results (TBI test), 22 (22%) were negative. A statistically significant association was found between positive biomarker profiles and CT-confirmed injuries (p<0.001). All patients with these CT-detected injuries also had positive TBI test.

The diagnostic performance of GFAP was assessed using ROC curve analysis. At a cutoff of 35.0 pg/mL, GFAP demonstrated 100% sensitivity, 52.24% specificity, and a negative predictive value of 100% for detecting CT-confirmed mTBI (Table 3, Figure1). Although GFAP showed perfect sensitivity, the moderate specificity led to a number of false positives. The positive predictive value was 52.24%, and diagnostic accuracy reached 68.63%. Similarly, UCH-L1 was evaluated using ROC analysis to determine diagnostic effectiveness. At a threshold of

Table 3. Contingency table and performance of serum Glial Fibrillary Acidic Protein (GFAP) Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) in detecting mild traumatic brain injury (mTBI) vs cranial CT

Performance metrics	UCH-L1 positive	UCH-L1 negative	GFAP positive	GFAP negative
CT positive	35	0	35	0
CT negative	40	27	32	35
Sensitivity	100 (90 - 100)		100 (90 - 100)	
Specificity	40.30 (28.49 - 53.0)		52.24 (39.67 - 64.60)	
NPV	100 (87.23 - 100)		100 (90 - 100)	
PPV	46.67 (41.82 - 51.58)		52.24 (45.99 - 58.42)	
Accuracy	60.78 (50.62 - 70.31)		68.63 (58.69 - 77.45)	

Values in the contingency table represent the number of patients (N). GFAP, Glial Fibrillary Acidic Protein; UCH-L1, Ubiquitin Carboxy-terminal Hydrolase L1; NPV, Negative Predictive Value; PPV, Positive Predictive Value

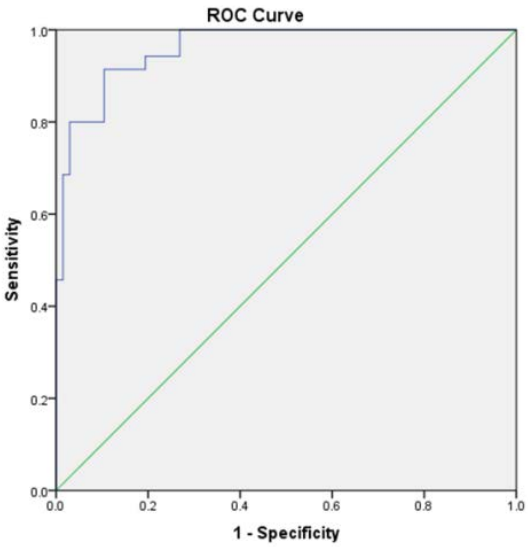

Figure 1. Receiver operating characteristic (ROC) curve showing performance of Glial Fibrillary Acidic Protein (GFAP) in detecting mild traumatic brain injury confirmed by cranial CT

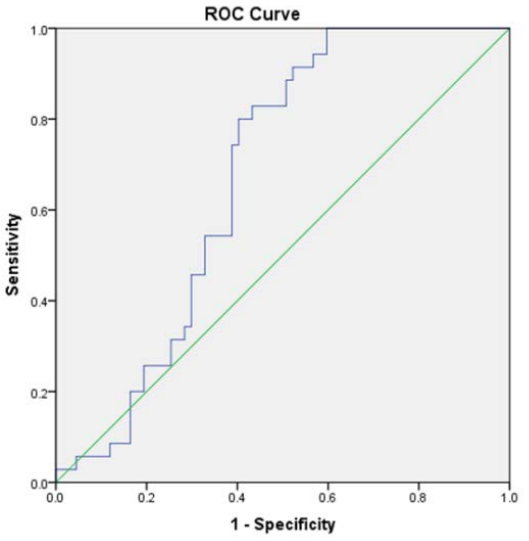

Figure 2. Receiver operating characteristic (ROC) curve showing performance of Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) in detecting traumatic brain injury confirmed by cranial CT

400.0 pg/mL, UCH-L1 achieved 100% sensitivity, 40.30% specificity, and NPV of 100% (Table 3, Figure 2)

DISCUSSION.

mTBI remains a diagnostic challenge because its clinical presentation is often subtle and non-specific, and conventional head CT is frequently normal even in patients with clinically relevant injury (1,5). Despite these limitations, CT has remained the primary imaging modality in routine practice, although its extensive use raises concerns about radiation exposure, overuse of healthcare resources and financial costs (18). These issues have intensified interest in non-invasive alternatives, particularly blood-based biomarkers, among which GFAP and UCH-L1 have emerged as leading candidates for mTBI evaluation (11,19).

In our cohort of 102 patients with mTBI, both GFAP and UCH-L1 were significantly inversely correlated with GCS, consistent with their role as markers of astrocytic and neuronal injury. GFAP showed a strong negative correlation (rho = −0.679, $p < 0.001$) and UCH-L1 a moderate negative correlation with GCS (rho = −0.362, $p < 0.001$), indicating higher biomarker levels in patients with lower consciousness scores. These results are consistent with prospective and multicentre studies reporting increasing GFAP and UCH-L1 concentrations with decreasing GCS and with CT-detectable intracranial lesions, even in clinically classified mTBI (6,11,19,20).

GFAP and UCH-L1 were positively correlated with each other (rho = 0.501, $p < 0.001$), supporting their complementary nature in capturing astroglial (GFAP) and neuronal (UCH-L1) injury, as highlighted in biomarker reviews and clinical validation studies (6,11,19). Correlations between biomarker levels and time from injury were weak, which is likely to reflect the narrow sampling window in our cohort (median 3.0 hours, IQR 2.0–4.0) within the 12-hour timeframe recommended by the manufacturer. This is consistent with kinetic studies showing that GFAP and UCH-L1 rise rapidly after trauma and remain diagnostically informative during the early post-injury phase, so variation with sampling time is limited when blood is drawn within the first hours after injury (6,19,20). Taken together, the strong correlations with GCS and minimal dependence on sampling time suggest that acute GFAP and UCH-L1 levels primarily reflect the burden of neuronal and astrocytic injury rather than the exact timing of blood sampling within this early window, supporting their potential use to identify patients with clinically relevant brain injury despite mild symptoms and to guide more selective use of head CT imaging (6,11,19,20).

In our single-centre study at UCC Tuzla, both GFAP and UCH-L1 demonstrated excellent diagnostic sensitivity (100%) and a negative predictive value of 100% for CT-positive intracranial lesions, supporting their use as rule-out tools. However, specificity was only moderate (52.24% for GFAP and 40.30% for UCH-L1), resulting in many biomarker-positive but CT-negative patients. A similar pattern was reported in the large multicentre ALERT-TBI trial, where combined GFAP/UCH-L1 testing with predefined, lower cut-off values (22 pg/mL and 327 pg/mL, respectively) in 1959 adults with TBI achieved high sensitivity (97.6%) and NPV (99.6%), but only modest specificity (11). Unlike ALERT-TBI, which included a broader spectrum of TBI severity, our study focused exclusively on adults with mTBI within 12 hours of trauma and applied higher decision limits (GFAP 35 pg/mL; UCH-L1 400 pg/mL). Across these methodological differences, the consistent pattern of very high sensitivity and NPV but limited specificity indicates that GFAP and UCH-L1 are particularly suited for ruling out clinically significant intracranial lesions, whereas positive results should be interpreted cautiously and always in conjunction with clinical assessment and neuroimaging.

Recent clinical and observational studies, together with meta-analyses, have further clarified the role of GFAP and UCH-L1 in mTBI, consistently showing higher biomarker concentrations in head-injured patients than in controls, with the greatest increases in those with CT- or MR-confirmed lesions and generally better discrimination for GFAP than for UCH-L1 (6,14,21–23). European cohorts of patients treated in hospital emergency departments, together with studies using rapid testing platforms, have additionally shown that combined measurement of these biomarkers provides high negative predictive value and supports early risk stratification in routine care (14,22–25). Contemporary reviews also note that including patients with orthopaedic or other extracranial injuries may reduce specificity, since mild biomarker elevations can occur without intracranial damage. However, such populations reflect real-world trauma practice, and available data indicate that the high NPV of GFAP and UCH-L1 for safely excluding clinically significant intracranial lesions is preserved (23–26).

Although the findings of this study are encouraging, several limitations should be acknowledged. It was a single-centre study with a relatively small sample, especially in the CT-positive group, which limits the precision and generalisability of the results. Major confounders such as polytrauma, anticoagulant therapy, known neurological disease and clinically significant intoxication were excluded, but patients with isolated orthopaedic or other extracranial injuries were included. These concomitant injuries may have modestly increased GFAP and UCH-L1 concentrations and contributed to the moderate specificity and the number of patients with elevated biomarker levels but no CT-detectable intracranial lesions. As brain MRI was not performed, we cannot determine whether such discordant results represent true false positives relative to CT or intracranial injuries that remain undetectable on CT. The study was not powered to compare biomarker performance between isolated head injury and additional extracranial trauma or to perform robust analyses by lesion type or prognostic outcome. Larger multicentre studies with integration of MRI findings and more detailed control of extracranial injuries and other confounders are needed to refine decision thresholds and to define the clinical scenarios in which these biomarkers provide the greatest benefit. Despite these limitations, this single-centre mTBI study showed that GFAP and UCH-L1 achieved excellent diagnostic sensitivity and a negative predictive value of 100% for excluding CT-positive intracranial lesions, supporting their use as rule-out triage tools to safely reduce unnecessary cranial CT in selected patients. However, their moderate specificity means that positive biomarker results should always be interpreted in conjunction with clinical assessment and neuroimaging, and further multicentre validation is required to better define the role of GFAP and UCH-L1 in mTBI management.

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TRANSPARENCY DECLARATION

Competing interest: None to declare.

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