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GFAP/UCH-L1 as a Biomarker for Rapid Assessment of Mild TBI in Emergency Departments

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Background: Traumatic brain injury (TBI) is a major cause of mortality and disability in Western countries. The diagnosis of TBI mainly involves computed tomography (CT), and Glasgow Coma Scale assessment. As frequent use of CT is associated with excessive radiation exposure, discovery of a biomarker for TBI could reduce unnecessary head CT scans. Thus, the main aim of this study was to evaluate a TBI assessment kit measuring glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), for its suitability to diagnose mild TBI in emergency departments (EDs).

Material/Methods: The records of 123 patients with head injuries admitted to the Clinical Emergency Department of the Regional Specialist Hospital in Olsztyn, Poland between December 2023 and August 2024, were prospectively analyzed. Patients underwent CT, were classified as isolated head injury (IHI, n=61) or injuries beside TBI (non-IHI, n=62), and tested for serum GFAP and UCH-L1 concentrations using immuno-chemical chemiluminescence.

Results: No significant differences in GFAP and UCH-L1 concentrations were observed between IHI and Non-IHI patients. While CT showed brain alterations in 7 patients, GFAP and UCH-L1 concentrations were above the threshold in 6 patients with brain injury confirmed by CT. The sensitivity of the TBI test was 83.3%, with specificity 29.1%. The sensitivity of GFAP was 83.3% and that of UCH-L1 was 50.0%, with specificities of 37.9% and 65.0%, respectively.

Conclusions: Based on our study, further investigations are required before GFAP and UCH-L1 blood test samples can be recommended as an adjunct to CT scans as a standard procedure.

Keywords: Biomarkers • Brain Injuries • Emergency Medical Services • Tomography, X-Ray Computed

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Introduction

Traumatic brain injury (TBI), caused by physical forces that alter brain function or cause other evidence of brain injury, is the leading cause of mortality and disability for people under the age of 45 in Western Europe and the United States [1,2]. Worldwide, 60-70 million people experience TBI each year [3,4]. TBIs contribute to an estimated global economic burden of $400 billion annually [4,5]. In the United States, yearly expenditures for non-fatal TBI are estimated to exceed $40 billion [6].

Based on the Glasgow Coma Scale (GCS), TBIs are classified as mild (mTBI) (13-15), moderate (9-12), and severe (8 or less) [7]. Approximately 80% of TBIs are classified as benign, self-healing injuries. However, 15-20% of mTBIs result in long-term disability, associated with post-concussion syndrome. While severe TBIs generate higher individual costs per patient, mTBI accounts for the majority of the total TBI cost [6].

It is possible to identify groups that have a higher incidence of TBIs. Such groups include elderly people, especially over 75 years of age, who have the highest rate of hospital admission and death due to TBIs, and homeless people, who are 2-4 times more likely to experience TBI and 10 times more likely to experience moderate or severe TBI, with 20.41% of head injuries involving loss of consciousness [3,8,9].

The initial diagnosis of TBI is difficult, because, in some cases, neurological symptoms associated with central nervous system damage do not become obvious for days or weeks, reducing the chances of prompt treatment [10]. Considering the epidemiology and cost, early diagnosis and severity assessment of TBI are critical to the well-being of patients.

The current clinical approach to treating head injuries consists of patient assessment, performing a computed tomography (CT) scan, and assessing for radiological markers of brain injury. However, structural post-traumatic lesions are detected only in 10-17% of patients presenting to the emergency department with mild head injury (GCS 13-15) [11-14]. There is a growing awareness of the redundant radiation exposure associated with undescriptive CT scans and the unnecessary diagnostic costs to the healthcare system [15]. Our experience demonstrates that repeated head trauma in a high-risk head injury group can result in more than 10 head CT scans within 2 years.

To date, many biomarkers have been evaluated as a 'brain troponin,' a potential screening test for brain tissue injury, with the advantage of being both rapid and safe. Promising results have been shown by a few markers of axonal injury, like neurofilaments, myelin basic protein, tau protein, and S100B protein [16]. The Abbott TBI kit has become commercially available. The present study assessed the potential of glial fibrillary acidic protein (GFAP) and ubiquitin L1 C-terminal hydrolase (UCH-L1) as rapid diagnostic tools for traumatic brain injury (TBI) in emergency departments (EDs). Introduction of a simultaneous UCH-L1 and GFAP lab test of patients with mild head trauma may at least partially reduce unnecessary head CT scans in patients with mTBI.

Glial fibrillar acid protein (GFAP) is a cytoplasmic protein located almost exclusively in astrocytes of the central nervous system [16]. Under normal conditions, this protein is also present in testicular tissue, including Sertoli cells, Leydig cells, and seminiferous tubules [17]. Ubiquitin L1 C-terminal hydrolase (UCH-L1), a soluble cytoplasmic protein of nerve cells, accounts for about 1-2% of soluble cytoplasmic proteins in the brain [16], but it is not exclusively brain-specific, as it has been found in the peripheral nervous system, specifically in neuromuscular junctions, and its expression has been observed in testis and ovary tissue [18,19].

Both proteins are secreted into the bloodstream within 1 hour after TBI. The maximum level of GFAP protein is reached approximately 20 hours after injury, and decreases up to 72 hours after injury. The GFAP remains at detectable low levels until 180 hours after injury [20]. UCH-L1 reaches peak serum concentrations from about 8 to 48 hours after injury, after which the protein is detectable with slight changes in concentration for 180 hours [20]. A systematic review established a positive correlation of high GFAP serum levels with post-traumatic intracranial structural changes confirmed via CT scan. The TRACK-TBI study demonstrated that elevated GFAP concentrations had greater sensitivity than head CT scans in the diagnosis of brain damage [20,21]. The CENTER-TBI study found that GFAP had the best predictive value for CT abnormalities up to 24 hours following injury, with an AUC of 0.89 [22]. UCH-L1 can very accurately predict post-traumatic structural abnormalities in CT, with sensitivity of 100% and specificity of 21-39% [22-24]. The combination of GFAP and UCH-L1 measurement with the cut-off points set at 327 pg/ml for UCH-L1 and 22 pg/ml for GFAP showed test sensitivity of 97.6% and negative predictive value of 0.996. In a study of 1959 patients, only 3 had positive CT results despite negative GFAP and UCH-L1 test results [25].

Material and Methods

Ethics Statement

The present observational study was approved by the local ethics committee of the University of Warmia and Mazury in Olsztyn (approval reference number 28/2023 dated 19 October 2023). The study was based on a prospective analysis of the medical records of patients hospitalized in the Clinical

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Emergency Department of the Regional Specialist Hospital in Olsztyn, Poland. Patients' medical records provided to the researchers were anonymized, with names and surnames being substituted by codes, and all the data collection methods followed the Helsinki Declaration. All patients included in this study provided written informed consent. The consent form informed patients about non-routine testing for GFAP and UCH-L1.

Study Participants and Inclusion Criteria

The initial study population comprised 140 patients who were admitted to the ED of the Regional Specialist Hospital between December 2023 and August 2024 in Olsztyn, but 17 patients were disqualified. Participants were divided into 2 groups: patients with only head injuries were classified as isolated head injury (IHI; n=61) and patients with additional injuries were classified as non-IHI (n=62).

The inclusion criteria were: head injury occurring less than 8 hours before admission, GCS score 13-15 at admission, and a qualified for head CT scan. Exclusion criteria were: age under 18 years, previous administration of murine monoclonal antibodies, previous positive rheumatoid factor test result, treatment with drugs containing intralipid within 24 hours before admission, treatment with acetylcysteine or calcium dobesylate during the last week before admission, previous hyperproteinemia, and blood bilirubin level >40 mg/dl.

Methods

On admission, the neurological status of the patients was assessed using the Glasgow Coma Scale (GCS) and blood serum levels of GFAP and UCH-L1 were tested. In addition, we considered demographic and clinical variables including sex, age, mechanism of injury, severity, comorbidities, coexisting injuries and systolic blood pressure.

A positive TBI test was defined as GFAP and/or UCH-L1 level beyond the cut-off point set at 35 pg/ml for GFAP and 400 pg/ml for UCH-L1, according to the manufacturer's instructions. Positive CT scan was defined as the presence of any structural post-traumatic lesion to the brain. All patients included in this study were qualified for a head CT scan according to the NICE head CT algorithm.

Sample Processing

Blood samples were collected in anticoagulant-free biochemical blood tubes and centrifuged (MPW-352R; MPW Med. Instruments, Poland), at 21 000× g for 10 min. Subsequently, the serum was transferred and stored at -20°C. Prior to analysis, the samples were thawed, brought to 20-25°C, and re-centrifugated at 21 000× g for 10 min.

Protein Measurement

Serum concentrations of GFAP and UCH-L1 were determined by the immunochemical chemiluminescence method (CMIA) using an Abbott Architect analyzer (Abbott, USA). For GFAP determination, the Abbott GFAP Reagent Kit 4W16 (Abbott, USA) with detection range of 6.1-42 000 pg/ml was used in accordance with the manufacturer's instructions. The UCH-L1 determination was carried out using the Abbott UCH-L1 Reagent Kit 4W18 (Abbott, USA), with detection range 26.3-25 000 pg/ml, in accordance with the manufacturer's instructions. To ensure the accuracy of the measurements, control specimens included with the reagent kits were used.

Statistical Analysis

The obtained data were analyzed using GraphPad Prism version 10.2.3 (GraphPad Software, USA) and the Statistica 12 statistical package (Tibco Software, USA).

Conventional descriptive statistics were used to present the categorical variables. Values are presented as means and standard deviation. The Shapiro-Wilk test was used to examine the normality of distribution of variables measurable with interval or ratio scales. In instances where the distribution of variables did not meet the assumptions of a normal distribution, the non-parametric Mann-Whitney U test was performed. The relationships between variables with nominal scales were estimated with the χ^2 test. The receiver operating characteristic curves reflecting the sensitivity and specificity of the assay to detect brain injury, and their specific area under the curve (AUC)s were calculated. $P<0.05$ was considered statistically significant.

Results

Out of 123 patients in the test group, 8 had to be hospitalized, 4 due to TBI and 4 due to other reasons. One patient in the study died, due to hemorrhagic stroke. CT abnormalities were found in 7 patients. Patients' characteristics are summarized in **Table 1**.

In the test group (n=123), 61 patients had isolated head injury (IHI), and 62 had other injuries besides TBI. The highest level of GFAP protein (1282.4 pg/ml) was in a 62-year-old patient with IHI and a negative CT scan, who previously had structural traumatic brain injury. The highest level of UCH-L1 protein (2475.6 pg/ml) was in 42-year-old patient with CT-negative head injury who was admitted to hospital following a high-speed car accident with additional hip injury. We found that 49 patients included in this study had non-traumatic brain abnormalities on CT, such as previous vascular lesions, meningiomas,

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Table 1. Characteristics of patients included in this study.

		All (n=123)	IHI	Non-IHI
Percentage (n)		100.0% (123)	49.6% (61)	50.4% (62)
Sex F [%(n)]		61.0% (75)	59.0% (36)	62.9% (39)
Age (Xmean/SD)		63.48/20.84	68.03/20.31	58.72/20.47
Comorbidities	None	26.8% (33)	19.6% (12)	33.9% (21)
	Alcohol dependency syndrome	3.3% (4)	6.6% (4)	0.0% (0)
	Pulmonary	7.3% (9)	6.6% (4)	8.1% (5)
	Oncological	4.1% (5)	3.3% (2)	4.8% (3)
	Neurological/psychiatric	11.4% (14)	13.1% (8)	9.7% (6)
	Nephrological	3.3% (4)	3.3% (2)	3.2% (2)
	Cardiovascular	52.8% (65)	60.7% (37)	45.1% (28)
	Metabolic	32.5% (40)	36.1% (22)	29.0% (18)
Additional injuries	None	49.5% (61)	100.0% (61)	0.0% (0)
	Soft tissue	10.6% (13)	0.0% (0)	21.0% (13)
	Bones	28.5% (35)	0.0% (0)	56.5% (35)
	Visceral organs	1.6% (2)	0.0% (0)	3.2% (2)
	Spine	21.1% (26)	0.0% (0)	41.9% (26)
Head wound		26.8% (33)	41.0% (25)	12.9% (8)

or degenerative changes to the brain tissue, and 42 of these patients had positive TBI test results, despite having a negative CT scan for injury. We also found that 1 person had negative TBI test result, despite a positive CT scan showing small brain tissue effusion.

Isolated Head Injury Vs Non-Isolated Head Injury

The comparison of GFAP serum level between the IHI and Non-IHI groups did not show any statistically significant differences (108.4±178.8 vs 70.7±78.6 pg/ml; p>0.05). Similarly, there were no significant differences in UCH-L1 serum level between the IHI and Non-IHI groups (402.0±349.5 vs 467.3±442.3 pg/ml; *P*>0.05) (**Figure 1**).

The CT-negative IHI and Non-IHI groups were compared. Despite the mean differences observed for GFAP (108.0±181.9 vs 68.89±78.7 pg/ml) and UCH-L1 (406.4±354.5 vs 434.8±400.7 pg/ml), these differences did not reach statistical significance (*P*>0.05). The distribution of this data is illustrated in **Figure 1**.

Sensitivity and Specificity

The overall sensitivity of the TBI test was 83.3% (95% CI 35.9-99.6%), with specificity 29.1% (95% CI 21.0-38.2). The isolated GFAP measurement demonstrated a sensitivity of 83.3% (95% CI 35.9-99.6%) and specificity of 37.9% (95% CI 52.1-70.4%). The isolated UCH-L1 measurement showed sensitivity of 50.0% (95% CI 11.8-88.19%) and specificity of 65.0% (95% CI 55.6-73.6%). For both measurements, the ROC curve was calculated (**Figure 2**). The area under the curve (AUC) for the GFAP measurement was 95.6% and 82.4% for UCH-L1. The specificity and sensitivity varied between age groups, as illustrated in **Table 2**. The number of patients was insufficient in all age groups to allow creation of an ROC curve. No statistically significant correlations were observed between symptoms present at admission and UCH-L1 level (*P*=0.345), GFAP level (*P*=0.265), and TBI test result (*P*=0.835).

Comorbidities and Other Injuries

In addition, we analyzed the correlation of other injuries and comorbidities with GFAP, UCH-L1, and TBI test sensitivity and specificity. The analysis showed that alcohol dependence syndrome, pulmonary diseases, and oncological diseases had no statistically significant correlation with GFAP, UCH-L1 levels, and TBI test results (*P*>0.05). Neurological/psychiatric disorders (*P*=0.037) and nephrological disorders (*P*=0.016) demonstrated a statistically significant association with UCH-L1 levels. Furthermore, metabolic comorbidities had a significant association with GFAP levels (*P*=0.002) and TBI test results (*P*=0.01). Cardiovascular comorbidities demonstrated a

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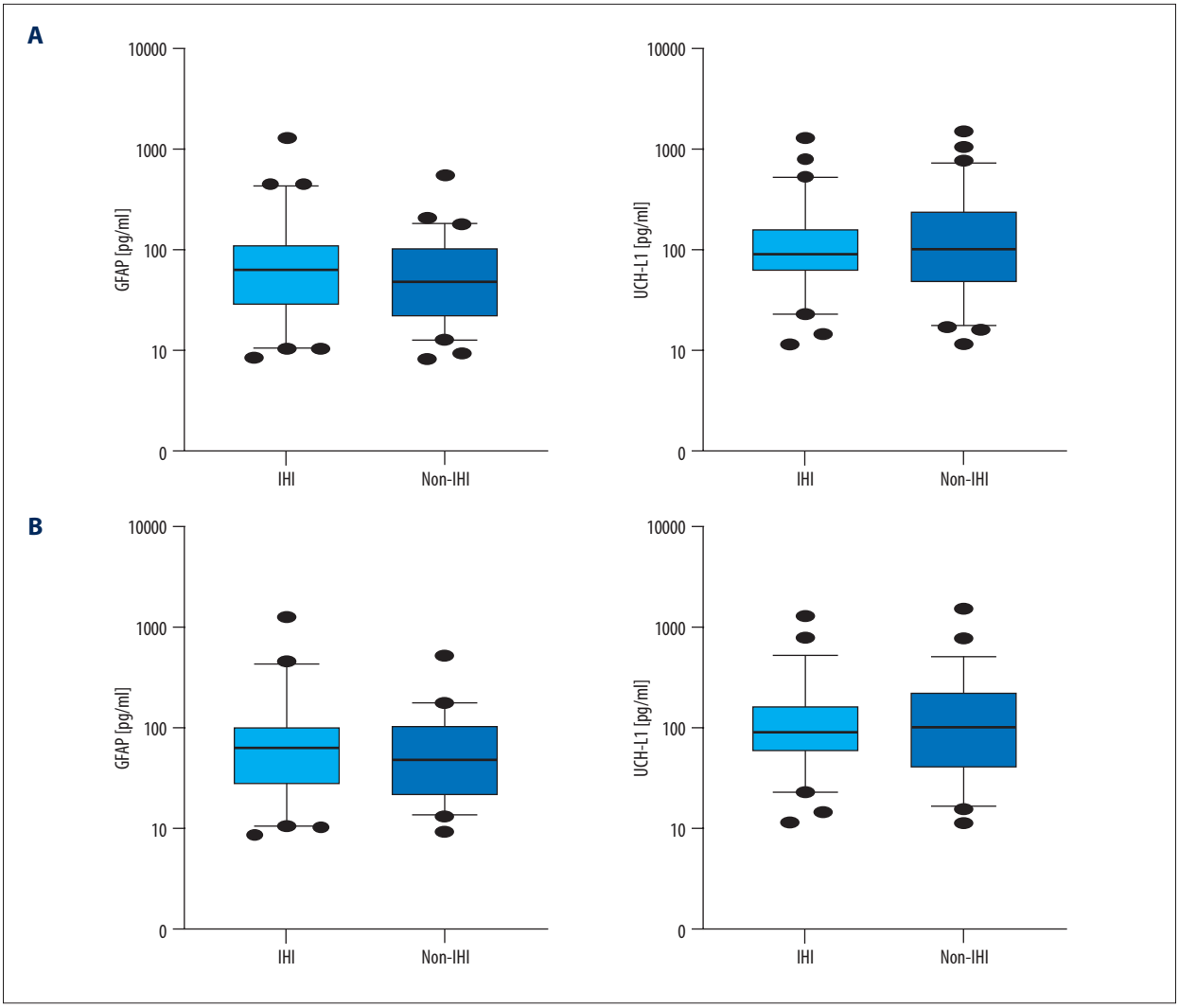

Figure 1. (**A**) Overall glial fibrillary acid protein (GFAP) and ubiquitin L1 C-terminal hydrolase (UCH-L1) level distribution. (**B**) CT-negative GFAP and UCH-L1 level distribution. Whiskers show 5-95% CI. A logarithmic scale was used to present results.

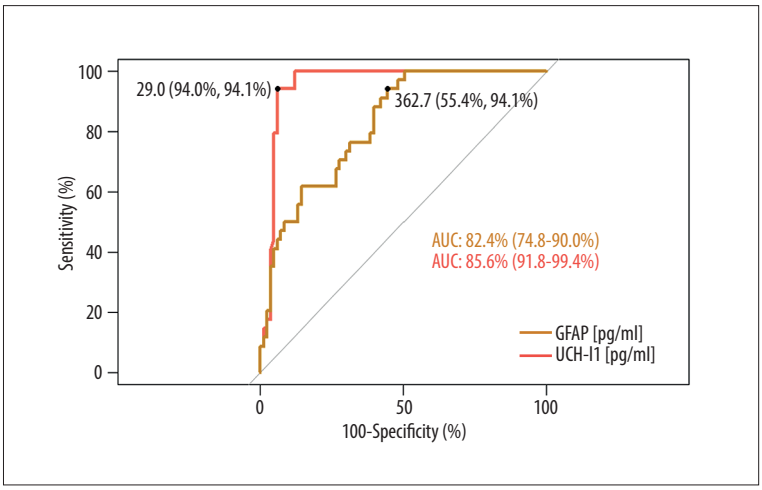

Figure 2. Receiver operating curve (ROC) for glial fibrillary acid protein (GFAP) and ubiquitin L1 C-terminal hydrolase (UCH-L1). Cut-off points were set at 35 pg/ml for GFAP and 400 pg/ml for UCH-L1

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Table 2. Sensitivity and specificity in age groups. Cut-off points were set at 35 pg/ml for glial fibrillary acid protein (GFAP) and 400 pg/ml for ubiquitin L1 C-terminal hydrolase (UCH-L1).

Age group	Test	Sensitivity	Specificity
18-40 years old	GFAP	0%	85.7%
	UCH-L1	0%	76.2%
	TBI	0%	66.7%
40-65 years old	GFAP	100%	45.9%
	UCH-L1	100%	75.7%
	TBI	100%	29.7%
>65 years old	GFAP	100%	14.0%
	UCH-L1	50%	51.7%
	TBI	100%	12.1%

Table 3. Sensitivity and specificity of tests.

	Test	Sensitivity	Specificity
Overall	GFAP	83.3%	37.9%
	UCH-L1	50.0%	65.0%
	TBI	83.3%	29.1%
Neurological/psychiatric disorders	UCH-L1	100.0%	76.9%
Nephrological disorders	UCH-L1		25.0%
Metabolic disorders	GFAP	100.0%	18.0%
	TBI	100.0%	15.4%
Cardiovascular disorders	GFAP	100.0%	20.3%
	UCH-L1	66.7%	60.7%
	TBI	100.0%	18.0%
Bone injuries	UCH-L1	100.0%	45.5%
Spine injuries	TBI	100.0%	48.0%

correlation with GFAP (P=0.004), UCH-L1 (P=0.018) and TBI test results (P=0.003). The sensitivity and specificity of the affected measurements are shown in **Table 3**.

Discussion

The overall TBI test specificity was 29.1%. In the ALERT-TBI study, the specificity was similar to ours, at 36.4% [25]. Notably, only 1 of 123 patients included in our study had a positive CT result with a negative TBI test. Consequently, our study demonstrates a sensitivity of 83.3%, which is lower than in the ALERT-TBI study (97.6%). The observed differences in study outcomes can be attributed to 2 main factors. Firstly, the study population was relatively small. Secondly, the ALERT-TBI study also included patients with GCS scores of 9-12 at the time of presentation. None of the patients included in our study required neurosurgical intervention, including a patient with a false-negative TBI result. However, all patients who were admitted due to TBI were identified by a positive TBI test result.

The specificity of the GFAP and UCH-L1 proteins is low, with a decline observed with increasing age. Elevated GFAP levels have been observed in patients with multiple sclerosis and neuromyelitis optica spectrum disorder, Alzheimer disease, and fronto-temporal lobar degeneration [26-30], which limits its use as an mTBI test in cognitively impaired older adults. Unintentional falls are the leading cause of ED visits, hospitalization, and mortality due to traumatic brain injury in individuals over the age of 64 in the United States and worldwide [3,31].

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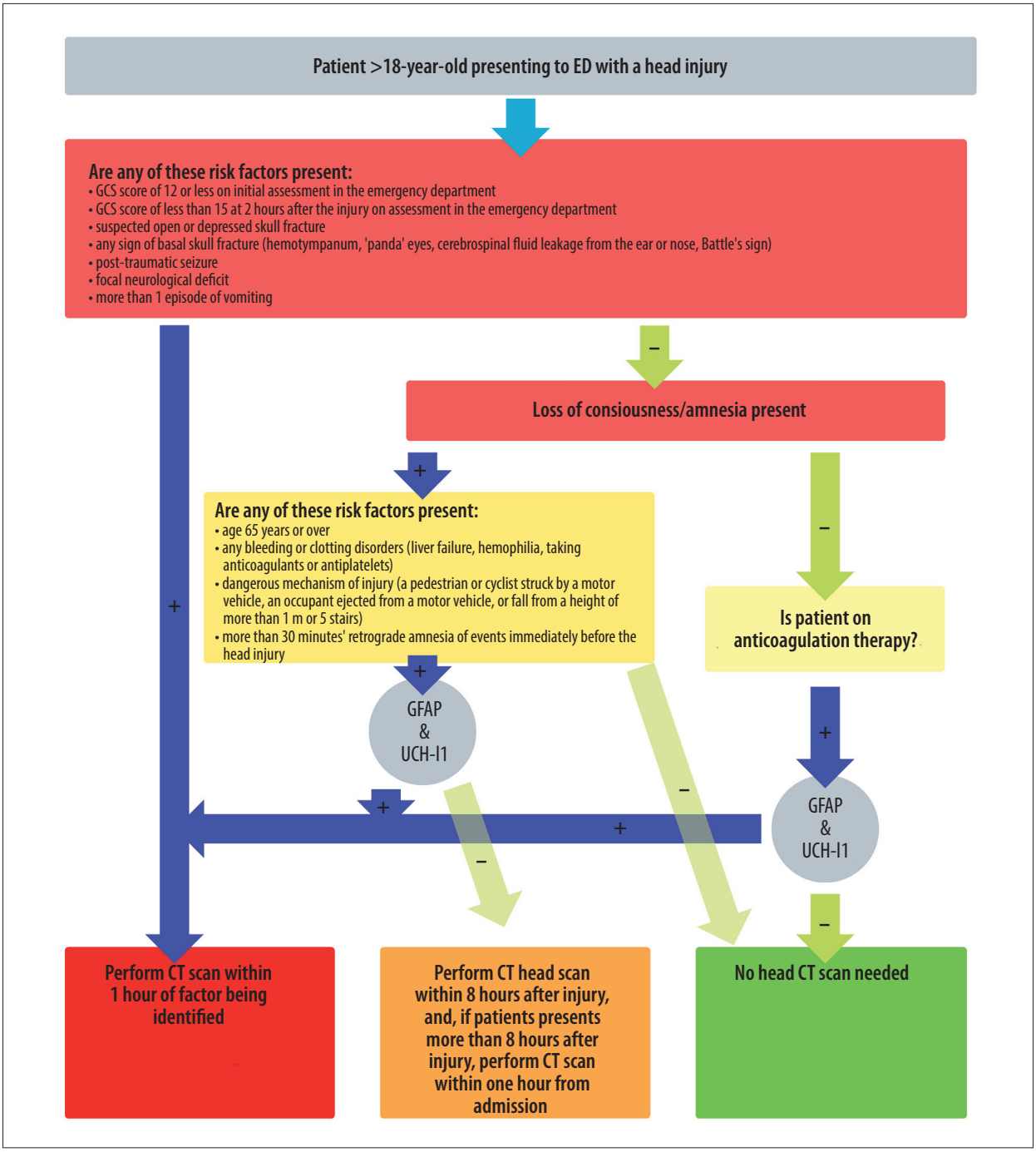

Figure 3. Proposed head injury diagnostic algorithm based on NICE 2023 Algorithm 1: selecting people age 16 and over for a CT head scan.

However, UCH-L1 is also altered in certain medical conditions. UCH-L1 is normally located almost exclusively in the central nervous system. However, after following thermal injury, serum levels of UCH-L1 increase and remain elevated for up to 7 days [32], which limits use of this biomarker in patients with coexisting burns. Expression of UCH-L1 rises in several malignancies [19,33]. Additionally, UCH-L1 blood levels are associated with cognitive function impairment as measured by the Mini-Mental Score Examination. This may be limiting factor, affecting sensitivity and specificity of measurements, particularly in older adults [34,35].

In our experience as emergency medicine physicians, many patients with head injury also have concomitant injuries, including

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damage to the bones, muscles, superficial soft tissues, and spinal cord. The presence of GFAP and UCH-L1 protein outside the central nervous system could be a limiting factor in the use of TBI test as a marker for traumatic brain injury. Our analysis shows a correlation between coexisting bone injury and UCH-L1 measurement, and there was a correlation between spine injuries and TBI results. GFAP protein is not a specific biomarker for brain injury, as GFAP levels were higher in cases of orthopedic injury than in CT-negative TBI cases, but this association was not noted for UCH-L1 protein [36]. Furthermore, it has been established that GFAP protein serum levels tend to be higher in patients with spinal cord injuries [37].

Despite the relatively low specificity of the GFAP and UCH-L1 simultaneous test, it was introduced to standard clinical practice in the United States. In 2018, the US FDA authorized the use of this 2-protein blood test for clinical purposes, and these proteins obtained the CE mark in Europe [3,38]. In 2024, the American College of Emergency Physicians (ACEP) guidelines permitted the utilization of GFAP and UCH-L1 brain injury biomarkers in patients with GCS scores of 14-15 at low risk for post-traumatic lesion on CT (assessed with scoring tools). Furthermore, the ACEP has recommended use of these 2 biomarkers in regions where the availability of CT is limited [39].

In our facility, head CT scan decisions are made based on the NICE head CT algorithm [40]. Based on the literature and the present results, we propose that GFAP and UCH-L1 biomarker measurement could be a helpful diagnostic tool in patients with mTBI when the algorithm suggests use of CT scanning but the clinical context is ambiguous. Furthermore, we propose using the UCH-L1 and GFAP test when a CT scan is recommended but must be postponed, with a positive result indicating an oligosymptomatic TBI and prompting the physician to expedite the diagnostic process. The adapted algorithm is presented in **Figure 3**.

The high negative predictive value and high sensitivity of simultaneous measurement of GFAP and UCH-L1 protein can be helpful when a difficult decision must be made regarding the performance of diagnostic imaging. For pregnant women, numerous guidelines advocate a risk and benefits assessment, in which the TBI test result can indicate whether the abandonment of CT scanning is safe for the mother. However, TBI test results facilitate assessment of the need for CT in patients requiring general anesthesia due to various reasons, thereby reducing the risk to the patient.

Our study has 2 principal limitations: the sample size was small and the measurements were conducted on preserved samples stored at low temperatures (certain proteins are susceptible to degradation during freeze-thaw cycles [41,42]).

Conclusions

The measurement of GFAP and UCH-L1 proteins has potential as a valuable diagnostic tool in the evaluation of head injury patients. However, the current body of evidence is insufficient to recommend it as a replacement for CT scans as a standard medical procedure in TBI. It is therefore recommended that further research be conducted on a larger patient cohort.

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Patient Consent

All patients included into this study signed patient consent declarations.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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