DOI: 10.59213/TP.2024.172
Trends in Pediatrics 2024;5(4):130-138

Original Article

Use of serum biomarkers in the diagnosis of traumatic brain injury

Nadira Nabiyeva Çevik[1], Ali Korulmaz[2], Mehmet Alakaya[3], Barış Ten[4], Çağrı Eroğlan[5], Mehmet Burak Yavuz Çimen[5], Ali Ertuğ Arslanköylü[3]

[1]Department of Allergy and Immunology, Hacettepe University Medical School, İhsan Doğramacı Children's Hospital, Ankara, Türkiye
[2]Department of Pediatric İntensive Care Unit, Kocaeli Derınce Educatıon and Research Hospıtal, Kocaeli, Türkiye
[3]Department of Pediatric Intensive Care, Mersin University Faculty of Medicine, Mersin, Türkiye
[4]Department of Radiology, Mersin University Faculty of Medicine, Mersin, Türkiye
[5]Department of Medical Biochemistry, Mersin University Faculty of Medicine, Mersin, Türkiye

This article derived from the thesis titled ''Use of Serum Biomarkers in the Diagnosis of Traumatic Brain Injury''conducted by Nadira Nabiyeva Çevik.

Cite this article as: Nabiyeva Çevik N, Korulmaz A, Alakaya M, et al. Use of serum biomarkers in the diagnosis of traumatic brain injury. Trends in Pediatrics. 2024;5(4):130-138.

ABSTRACT

Objective: Traumatic brain injury (TBI) is a leading cause of death and disability in the pediatric age group. This study aimed to investigate the effectiveness of serum S100 calcium-binding protein B (S100b), ubiquitin carboxyterminal hydrolase-like1 (UCH-L1), glial fibrillary acidic protein (GFAP), and neurofilament (NF) protein levels in predicting the diagnosis and prognosis of traumatic brain injury.

Methods: The research comprised head trauma patients aged 1 month to 18 years hospitalized at Mersin University Faculty of Medicine between October 2018 and November 2019. We recorded the demographic data of the patients, the type of trauma, the treatments administered in the pediatric intensive care unit (PICU), the Glasgow Coma Scale (GCS), the Pediatric Trauma Score (PTS), and the computed cerebral tomography (CT) reports. S-100b protein, UCHL-1, GFAP, and NF levels of the patients and control group were checked. The correlation between serum levels of biomarkers and GCS, CT findings, Rotterdam score, and Glasgow Outcome Scale-Extended (GOS-E) score of the patients was analyzed statistically.

Results: The study included 73 patients, 49 males and 24 females. Comparing the groups revealed no statistically significant correlation between GFAP and TBI ($p>0.05$). However, the correlation between S-100b, UCHL-1, and NF and patient groups was statistically significant ($p<0.05$). The NF level was statistically higher in the PICU 24-hour group than in the control and pediatric emergency groups but statistically lower compared to the PICU 48-hour group ($p<0.05$). UCHL-1 levels in the PICU 24-hour group were statistically higher than those in the control group ($p<0.05$). The inverse correlation between GOS-E and UCHL-1 in the PICU 24-hour group was statistically significant ($p<0.05$). Patients with CT findings had a higher UCHL-1 level than those without ($p<0.05$).

Conclusion: S-100b, UCHL-1, and NF may be used for the diagnosis of TBI and evaluation of its severity. Furthermore, UCHL-1 has the potential to be useful in forecasting patients' prognoses.

Keywords: traumatic brain injury, biomarkers, glial fibrillary acidic protein, ubiquitin carboxyterminal hydrolase-like1

Correspondence: Nadira Nabiyeva Çevik **E-mail:** nadiyanabiyeva@gmail.com
Received: 23.07.2024 **Accepted:** 14.12.2024

INTRODUCTION

Traumatic brain injury (TBI) is defined as the disruption of brain functions caused by a physical force applied to the head. There may be cases of isolated head trauma, but there are also cases of trauma accompanied by head trauma in which multiple organ systems are affected.[1] Injury mechanism can be defined as the relation of physical and physiological effects resulting from mechanical forces on the head with the brain.[2] Hypoxia, hypotension, cerebral edema, and increased intracranial pressure over the initial injury cause the secondary damage.

With cell death on the first day after TBI and disruption of the blood-brain barrier, proteins that can trigger the immune response and their degradation products (biomarkers) are released from damaged cells into the cerebrospinal fluid (CSF) and blood.[3] Neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100b), myelin essential protein (MBP), ubiquitin carboxyterminal hydrolase-like 1 (UCH-L1), and neurofilament (NF) proteins are some of the biomarkers that have been found in human biofluids after TBI.[4,5] The Rotterdam score, Glasgow Coma Scale (GCS), Pediatric Trauma Score (PTS), and Glasgow Outcome Scale-Extended (GOS-E) are used to evaluate and follow-up patients with TBI. GOS-E is a scoring system used in regular neurological examinations of patients with head trauma and in monitoring their recovery levels. This assessment score evaluates the patient's activities of daily living, social relationships, and professional performance. It is scored from 1 to 8, from worst to best.[6] Serum-based TBI biomarker tests can assess the degree of TBI severity and predict patient prognosis by correlation with other neurological measures (neuroimaging). There is a need for rapid and straightforward diagnostic serum markers that can reduce the use of CT and may be used for the diagnosis and follow-up of patients with TBI. An appropriate marker should be readily available, increase the severity of trauma in the acute phase compared to the control group, be at basal levels in the healthy control group, originate mainly from the damaged brain, and be easily identified and measured using available tests. It should also be sensitive to TBI severity defined by GCS and CT abnormalities, allowing repeated detections within 48 hours of brain injury.[7] Our knowledge about serum biomarkers in the diagnosis and follow-up of TBI in children is minimal. Our study aims to demonstrate the effectiveness of S-100b protein, UCHL-1, GFAP, and NF levels in diagnosing TBI and predicting the prognosis of TBI patients admitted to the pediatric emergency department and pediatric intensive care unit (PICU).

MATERIAL and METHODS

Sample size calculation was performed prior to the study. Using a significance level (α) of 0.05, power (1-β) of 0.80, and expected difference in biomarker levels between TBI and control groups of 40% based on previous studies, the minimum required sample size was calculated as 53 patients and 20 controls. In this prospective study, 53 children with head trauma aged one month to 18 years who were admitted to the pediatric emergency room and PICU of Mersin University Medical Faculty Hospital between October 2018 and November 2019 were included, along with 20 healthy children in the same age group as the control group. The participants were divided into two groups: those monitored in the PICU (n = 15) and those attended to in the emergency department (n = 38). The age, gender, physical examination findings, laboratory parameters, kind of trauma, length of hospital stay, need for mechanical ventilation, blood transfusion, therapies, and radiological results of the patients were recorded. The Rotterdam score, GCS, and PTS of the patients were calculated. The GOS-E scale was calculated and recorded 12 months after the discharge of the patients hospitalized in the PICU. Blood samples were taken from the patients at admission to measure serum S-100b protein, UCHL-1, GFAP, and NF biomarker levels. The measurement of biomarkers was repeated at 48 hours of trauma in patients followed up in the PICU. A group named "PICU 48-hour" was created from these measurements. The patients in the control group were composed of healthy individuals who do not have a history of smoking, alcohol, or drug use, have no acute traumatic injury, have not followed a special diet in the last three months, have not had a critical illness in the previous month, have not undergone radiological examination such as x-ray or tomography, and have not been vaccinated. The study patients underwent cerebral CT procedures based on their clinical indications. The same radiologist who performed the Rotterdam scoring also evaluated the cerebral CTs and recorded the results.

5 ml of venous blood samples taken from the patients and the control group to measure S-100b protein, UCHL-1, GFAP, and NF levels were placed in the EDTA tube for hematological examination. In contrast, gel tubes were used for biochemical analysis. S-100b protein, UCHL-1, GFAP, and NF biomarkers were placed into gel tubes in the first 24 hours and 48 hours of our study, and the samples were centrifuged for 15 minutes, and their serums were separated. The serum samples were stored in the biochemistry laboratory of our hospital under specific conditions, at a temperature of -80 ºC, until the start of the research. The samples were analyzed using human NEFL (neurofilament light polypeptide) (lab science, catalog no. E-EL-H0741), human GFAP (glial fibrillary acidic protein) (lab science, catalog no. E-EL-H6093), human S100B (S100 calcium-binding protein B) (lab science, catalog no. E-EL-H1297), and human UCHL1 (ubiquitin carboxyterminal hydrolase L1) (lab science, catalog no. E-EL-H2377) using the Sandwich-ELISA method on an automated ELISA analyzer (DSX, Dynex Technologies, USA).

Statistical analysis

The SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were expressed as numbers and percentages, and continuous measurements were expressed as mean and standard deviation (median and minimum-maximum, where necessary). The Shapiro-Wilk test was applied to determine whether the parameters in the study showed a normal distribution. Independent student t-tests and one-way ANOVA tests were used for normally distributed parameters, while Mann-Whitney U and Kruskal-Wallis tests were used for non-usually distributed parameters. The Bonferroni test, one of the post-hoc tests, was used to determine the source of the difference between the groups. In all tests, the accepted level of statistical significance was 0.05. This study was authorized by the Mersin University Ethics Committee on November 7, 2018, with the decision numbered 2018/452, and was financed by the Scientific Research Projects Coordination Unit of Mersin University, under project number 2019/-1-TP3-3347.

RESULTS

The study included 73 cases, 53 in the patient and 20 in the control groups. There were 15 patients in the PICU group and 38 patients in the pediatric emergency group. It was determined that there was no statistically significant difference between the ages and genders of the patients included in the study and the control group (p > 0.05) (Table 1).

Table 2 shows the mechanical ventilator (MV), inotrope and transfusion requirement, length of stay in the PICU, length of MV, and 24-hour and 48-hour GCS and GOS-E values of the patients followed in the PICU. The majority of patients in the PICU received MV, inotropic, and transfusion support.

No statistically significant difference was found between the trauma causes and survival rates of the PICU and pediatric emergency group patients (p> 0.05). However, the differences between the two groups in terms of antiedema and antiepileptic treatment, surgery, length of hospital stay, and additional disease presence were statistically significant (p<0.05). All patients hospitalized in the PICU received antiedema treatment, but only 7.9% of patients in the pediatric emergency department received it. Falling (33.3%) and road traffic accidents (33.3%) were the most common causes of trauma among the patients in the PICU. In comparison, the majority of the patients in the pediatric emergency room were found to be falling (73.7%) (Table 3).

There was no statistically significant difference between the patients in the PICU and pediatric emergency in C-reactive protein (CRP), platelet, sodium, and potassium values (p > 0.05). It was found that patients who followed up in the PICU had statistically significantly higher leukocyte and blood glucose levels and statistically considerably lower hemoglobin and hematocrit levels compared to the patients in the pediatric emergency department (p<0.05). The information is shown in Table 4.

The cerebral CT findings and consciousness status of the PICU patient group were compared with those of the emergency patient group. A cerebral CT evaluation was performed according to the Rotterdam scoring. The study detected pathological findings in cerebral CT in 58.5% (n = 31) of the patients. The incidence of pathological cerebral CT findings was 93.3% in the PICU group and 44.7% in the pediatric emergency group, and this difference was statistically significant (p<0.05). The ratio of patients with moderate and severe TBI was statistically significantly higher in the PICU group than in the pediatric emergency group (p<0.05).

Similarly, the difference between both groups regarding PTS was statistically significant (p<0.05). While PTS was <8 in the majority of patients (71.4%) in the PICU group, PTS was >8 in the majority of pediatric emergency patients (92.1%). In addition, when the mean values of GCS, PTS, and Rotterdam scoring were examined, the difference between the two groups was

Table 1. Patient age and gender distribution by group

		PICU (n: 15)		Control (n: 20)		Pediatric Emergency (n: 38)		Total (n: 73)		p*
		n	%	n	%	n	%	n	%	
Gender⁺	Female	3	20.0	10	50.0	11	28.9	24	32.9	0.132
	Male	12	80.0	10	50.0	27	71.1	49	67.1	
Age (month) (x^2)		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p*
		137.26±72.55 (9-204)		84.55±72.32 (7-215)		95.21±63.21 (3-204)		100.93±69.45 (3-215)		0.145

x^2: Kruskal-Wallis test; ⁺: Chi-square; PICU; Pediatric Intensive Care Unit; min: minimum; max: maximum, *p<0.05

Table 2. Clinical parameters of patients admitted to the PICU

		Number (n)	Percent (%)
Mechanical Ventilator Support	no	10	66.7
	yes	5	33.3
Inotrope	no	13	86.7
	yes	2	13.3
Transfusion	no	11	73.3
	yes	4	26.7
GCS at 24th hour× (TBI level)	severe	5	33.3
	moderate	5	33.3
	mild	5	33.3
GCS at 48th hour× (TBI level)	severe	5	33.3
	moderate	1	6.7
	mild	9	60.0
		Mean±SD	**min-max**
Length of stay in the PICU (hours)		179.20±159.67	24-624
Mechanical Ventilator Support (day)		2.73±4.14	0-10
GOS-E		6.00±1.81	1-8

GCS; Glasgow Coma Scale, GOS-E; Glasgow Outcome Scale Extended, MV; Mechanical ventilator, PICU; Pediatric
Intensive Care Unit, TBI; traumatic brain injury ×: Severe;8 and below, Moderate;9-13, Mild;14-15; min: minimum; max: maximum

statistically significant (p<0.05). The mean Rotterdam score was higher in the PICU patient group, but the mean GCS and PTS were higher in the pediatric emergency patient group (Table 5).

When the relationship between the presence of cerebral CT findings and the mean values of UCHL-1, GFAP, S100b, and NF in the patients in intensive care and emergency groups was investigated, a statistically significant relationship was found between patients with pathological findings on cerebral CT and a high mean value of UCHL-1 (p<0.05), on the other hand, no correlation was found with GFAP, S-100b, and NF and CT findings. Although the mean values of NF and S-100b were higher in patients with cerebral CT findings than those without, the difference was not statistically significant (Table 6). It was also found that there was an inverse correlation between GOS-E results and all biomarkers in PICU patients in the 24-hour group. However, only the inverse correlation with UCHL-1 was statistically significant among these parameters (p<0.05). However, we found no statistically significant correlation between GOS-E findings and biomarkers in the PICU 48-hour patient group.

The correlation between S-100b protein, UCHL-1, GFAP, and NF parameters of the PICU patients at 24 hours and 48 hours in the pediatric emergency and control groups was examined. Differences between groups in GFAP levels were not statistically significant (p > 0.05). On the other hand, the differences between the groups in S-100b protein, NF, and UCHL-1 values were statistically significant (p<0.05). S-100b protein and UCHL-1 were highest in the PICU 24-hour patient group, while NF was highest in the PICU 48-hour patient group (Table 7).

DISCUSSION

This prospective study is one of the few investigations to simultaneously evaluate multiple serum biomarkers (S-100b, UCH-L1, GFAP, and NF) in pediatric TBI patients. Our primary objective was to assess the effectiveness of these biomarkers in diagnosing TBI and predicting patient outcomes. The main outcomes indicate that S-100b and UCH-L1 reach their peak within 24-hours following damage, whereas NF levels persist in ascending for up to 48 hours. UCH-L1 had a substantial connection with CT results and GOS-E scores, indicating its potential utility as a diagnostic and prognostic instrument in pediatric TBI.

TBI may result in both temporary and chronic deficits in cognitive, physical, and psychosocial functioning. These impairments are often accompanied by a reduction or alteration in the state of awareness.[8] Impaired cerebral perfusion after TBI leads to disturbed cerebral oxygenation, causing brain hypoxia. Hypoxia occurs when there is a disequilibrium between the amount of oxygen being delivered to the brain and the amount of oxygen being used by the brain.

We investigated gender and trauma type as factors affecting TBI severity. A study that included 59 children aged 0–19 years found that the differences in terms of age and gender were not statistically significant.[9] Also, our study determined that the gender and age differences between the patient groups were not statistically significant. However, the mean age of the patients followed in the PICU was higher than the patients followed in the emergency department, which was attributed to the increased risk of exposure to severe trauma with age. When the types of trauma-causing TBI were examined, it was reported that the most common cause of trauma in the current population was a road traffic accident, followed by falling.[10] In our study, unlike the literature, fallings (62.3%) were in the first place, followed by motor vehicle accidents (28.3%) and other causes. The location, socioeconomic status, and lifestyle differences may explain this inconsistency with the literature.

Table 3. Comparison of clinical features of PICU and Pediatric Emergency Group patients								
		PICU (n:15)		Pediatric Emergency (n:38)		Total (n:53)		p
		n	%	n	%	n	%	
Cause of trauma	Road traffic accident (RTA)	8	53.3	7	18.5	15	28.3	0.031
	Trauma	5	33.3	30	79	35	66.1	
	Brunt	0	0.0	1	2.6	1	1.9	
	Work accident	1	6.7	0	0.0	1	1.9	
	Suicide	1	6.7	0	0.0	1	1.9	
Survival	Non-survival	1	6.7	0	0.0	1	1.9	0.108
	Survive	14	93.3	38	100.0	52	98.1	
Anti-edema treatment	no	0	0.0	35	92.1	35	66.0	**0.000**
	yes	15	100.0	3	7.9	18	34.0	
Antiepileptic drug	no	1	6.7	36	94.7	37	69.8	**0.000**
	yes	14	93.3	2	5.3	16	30.2	
Surgery	no	8	53.3	38	100.0	46	86.8	**0.000**
	yes	7	46.7	0	0.0	7	13.2	
Comorbidities	no	6	40.0	29	76.3	35	66.0	**0.012**
	yes	9	60.0	9	23.7	18	34.0	
		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p
Length of hospital stay (hours)[u]		244.0±178.31 (48-708)		18.84±29.11 (4-120)		82.56±140.17 (4-708)		**0.000**

*p<0.05, u: Mann-Whitney U test, PICU; pediatric intensive care unit; min: minimum; max: maximum

Table 4. Comparison of Laboratory Findings of the PICU and Pediatric Emergency Group				
	PICU (n:15)	Pediatric Emergency (n:38)	Total (n:53)	p
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
Leukocyte	19.55±7.88	10.73±3.86	13.23±6.59	**0.000**
($x10^3$/µL) (u)	(8.48-33.64)	(4.46-23.59)	(4.46-33.64)	
CRP	4.25±9.96	8.46±16.68	7.27±15.11	0.053
(mg/L) (u)	(0.1-38.5)	(0-98)	(0-98)	
Hgb	10.41±2.35	12.23±1.32	11.72±1.85	**0.002**
(g/dL) (t)		(9.5-14.5)	(6.9-15.7)	
Hct	30.26±7.13	35.52±3.95	34.03±5.52	**0.001**
(%) (t)		(25-42)	(20-48)	
Platelet	288.8±101.79	291.84±88.27	290.98±91.30	0.629
(x103/µL) (t)	(152-542)	(100-457)	(100-542)	
Sodium	137.86±3.46	137.70±3.03	137.75±3.12	0.524
(mmol/L) (u)	(129-143)	(130-145)	(129-145)	
Potassium	3.98±0.48	3.99±0.44	3.99±0.45	0.843
(mmol/L) (t)	(2.76-4.82)	(3.16-4.74)	(2.76-4.82)	
Serum glucose levels	207.13±137.52	129.32±51.10	151.34±90.56	**0.017**
(mg/dL) (u)	(99-592)	(83-380)	(83-592)	

* p<0.05, t: independent student test, u: Mann- Whitney U test, PICU: Pediatric Intensive Care Unit, CRP: C-reactive protein, Hgb: Hemoglobin, Hct: Hematocrit; min: minimum; max: maximum

Table 5. Comparison of cerebral CT findings and GCS, PTS, and Rotterdam CT scoring results in PICU and Pediatric Emergency Group patients

		PICU (n:15)		Pediatric Emergency (n:38)		Total (n:53)		p
		n	%	n	%	n	%	
CT finding (k)	no	1	6.7	21	55.3	22	41.5	**0.001**
	yes	14	93.3	17	44.7	31	58.5	
GCS (k)	severe	5	33.3	0	0.0	5	9.4	**0.000**
	moderate		5	33.3	3	7.9	8	
	mild	5	33.3	35	92.1	40	75.5	
PTS (k)	< 8	10	71.4	3	7.9	13	25.0	**0.000**
	> 8	4	28.6	35	92.1	39	75.0	
		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p
Rotterdam CT scoring (u)		1.40±0.73 (0-3)		0.97±0.28 (0-2)		1.09±0.49 (0-3)		**0.005**
GCS (u)		10.46±5.13 (3-15)		14.44±0.82 (11-15)		13.32±3.29 (3-15)		**0.001**
PTS (u)		5.40±3.56 (0-11)		10.5±1.08 (8-12)		9.05±3.10 (0-12)		**0.000**

*p<0.05, u: Mann-Whitney U test, k: Chi-square, PICU: Pediatric Intensive Care Unit, PTS: Pediatric Trauma Score, GCS: Glasgow Coma Score, Severe; 8 and below; Moderate; 9–13, Mild; 14–15; CT: computer tomography

Table 6. Correlation of biomarkers with cranial CT and GOS-E

Biomarker(s)	Cerebral CT finding			GOS-E			
	no (n: 23)	yes (n:30)	p	PICU-24		PICU-48	
	Mean±SD	Mean±SD		r	p	r	p
GFAP (pg/ml)	360.96±160.32	319.28±210.61	0.434	-0.226	0.419	0.334	0.224
S-100b (pg/ml)	755.32±560.96	1011.66±605.19	0.121	-0.116	0.680	-0.361	0.186
NF (pg/ml)	2.79±9.72	4.25±8.48	0.564	-0.245	0.380	-0.356	0.193
UCHL-1 (pg/ml)	323.07±1032.7	1467.76±2190.46	**0.025**	-0.633	**0.011**	0.146	0.603

GFAP: glial fibrillary acidic protein; S-100β: S100 calcium-binding protein B, UCHL-1; Ubiquitin carboxy-terminal hydrolase L1, NF; Neurofilament protein, GOS-E; Glasgow Outcome Scale Extended, PIC-24; Pediatric intensive care 24-hour patient group, PIC-48; Pediatric intensive care 48th hour patient group

Radiological imaging techniques and a neurological examination of the patient are the main methods used to diagnose TBI. The GCS is the most commonly used scale for evaluating neurological tests. A GCS score of 13–15 defines mild TBI, 9–12 moderate TBI, and 3–8 severe TBI.[11] A study examined the GCS and found that 26% of the patients had moderate or severe TBI, while 74% had mild TBI.[12] Şimşek et al. reported a rate of moderate and severe head trauma at 29.9% in their study.[13]

Most patients in our study had mild TBI, accounting for 75.5% of the cases, which aligns with the findings reported in existing literature. Recent enhancements in PICU infrastructure and a greater supply of trained healthcare workers, especially pediatric emergency and intensive care experts, have led to decreased fatality rates from TBI. The mortality rate of our study, 1.9%, is consistent with the current literature's reported figure of 3.8%.[12,14] A research conducted by Lazar et al. revealed that children with mild TBI had lower levels of serum sodium and potassium and greater levels of serum glucose and leukocytes compared to healthy individuals.[15] In our study, the leukocyte and serum glucose levels of the patients admitted to the PICU were higher than those followed in the pediatric emergency room. Both our study and the study of Lazar et al. show an increase in leukocyte and serum glucose levels as the severity of TBI increases. In other words, hyperglycemia and leukocyte levels are essential parameters in identifying the severity of TBI. When planning follow-up and treatment for trauma patients, these factors should be considered. In addition, since hyperglycemia is associated with increased mortality after TBI, it is crucial to keep blood glucose within physiological limits in these patients. PTS and GCS are valuable tools for evaluating the severity of trauma in pediatric patients. GCS is the most widely used scale to measure the severity of TBI in adults and children after a modification.[16,17] A study investigating the

Table 7. Investigation of the correlation of biomarkers between PICU, pediatric emergency, and control groups				
	GFAP (pg/ml)	S100b (pg/ml)	NF (pg/ml)	UCHL1 (pg/ml)
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)
PICU 24th hour (n:15), (1)	380.67±255.71	1291.55±619.24	5.67±10.30	1518.27±2203.81
	(12.75-720.52)	(247.30-3163.04)	(0.00-27.73)	(0.00-5000.0)
Control (n:20), (2)	348.99±196.55	925.67±552.48	1.07±1.84	57.92±130.75
	(41.33-651.33)	(101.82-1781.29)	(0.03-5.49)	(0.01-472.01)
Pediatric Emergency (n:38) (3)	320.28±157.67	746.03±515.45	2.80±8.41	754.99±1687.65
	(39.46-659.60)	(25.60-1689.25)	(0.18-47.01)	(0.00-5000.0)
PICU 48th hour (n:15), (4)	380.35±214.83	719.44±544.76	63.79±95.56	422.34±1269.60
	(12.78±654.77)	(25.72-1731.73)	(0.37- 284.21)	(0.01-5000.0)
Total (n: 88)	347.34±194.05	875.31±575.38	13.29±45.27	669.97±1574.76
	(12.75-720.52)	(25.6-2163.05)	(0.0-284.21)	(0.0-5000.0)
P	0.663	**0.021**	**0.000**	**0.027**
Post-hoc significance p	No significant difference between groups	1-4; p=0.032 1-3; p=0.009	4-1; p=0.001 4-2; p=0.000 4-3; p=0.000	1-2; p=0.038

* p<0.05, x2: Kruskall-Wallis test, F: one-way Anova, Post Hoc: Bonferroni, PICU: Pediatric Intensive Care Unit, GFAP: glial fibrillary acidic protein, S-100β: S100 calcium-binding protein B, UCHL-1: ubiquitin carboxy-terminal hydrolase L1, NF: neurofilament protein

effectiveness of PTS and GCS in predicting mortality in children injured by trauma reported that the mean GCS and PTS were higher in children who were non-survival.[10] Since the mortality rate was not sufficient for statistical evaluation in our study, this comparison was performed between the pediatric emergency group and the PICU group with different TBI severity. In our study, the mean GCS and PTS were found to be 10.4 and 5.4 in the PICU group and 14.4 and 9.05 in the pediatric emergency group, respectively. Both in the literature study and our study, we observed that scores in both scoring methods decreased as the severity of TBI increased. In Papa et al.'s investigation, it was shown that patients with TBI who had intracranial lesions on a cranial CT scan had substantially elevated levels of UCH-L1 in their blood, compared to individuals without lesions[18] Consistent with previous research, our study found that serum UCH-L1 levels were significantly elevated in individuals with CT results compared to those without CT findings. Our investigation revealed a negative association between the GOS-E results and the UCH-L1 level of the patients in the PICU. This finding indicates that the neurological outlook of patients may be anticipated by assessing the UCH-L1 levels of patients who are monitored in the PICU for TBI. Furthermore, based on the findings of our research and the study conducted by Papa et al.[18] it can be concluded that UCH-L1 serves as a reliable indicator for detecting TBI during the first 24-hour period. GFAP, which Eng described in 1971, is a monomeric small and acidic intermediate protein found in the astroglial skeleton and is a brain-specific marker after cell death.[19] In a study conducted in patients with and without head trauma, serum GFAP, S100b, and NSE levels were evaluated, and it was shown that GFAP has higher specificity in head trauma than other biomarkers (S100b, NSE).[20] Lei et al. reported that GFAP peaked at 0.5–4 hours after injury.[21] Similarly, Papa et al. observed that GFAP was detected in the serum immediately after injury, distinguishing patients with head trauma from others. The serum GFAP level was higher in patients with mild TBI who had lesions on CT than in those without.[22] Our research did not detect any statistically significant difference in the GFAP values between PICU and pediatric emergency patients, regardless of whether they had CT results or not. The explanation for this was hypothesized to be the potential oversight of the peak phase of GFAP in our investigation since some blood samples were collected more than 4 hours after the incident. S100b is a serum biomarker that has been extensively researched in TBI. It is a protein that binds to calcium channels and is found in high levels in astroglial cells in brain tissue.[23] A previous investigation revealed that the average blood S100b level in patients with severe TBI was considerably greater than that in individuals with mild TBI.[24] In our study, the differences between the groups were found to be statistically significant. This difference was because the biomarker level in the PICU 24-hour group was higher than the pediatric emergency, control, and PICU 48-hour groups. This finding indicates that the S100b concentration increases during the first 24-hours after a severe head injury and returns to a normal level after this period. Both our research and the study

conducted by Abbasi et al.[24] corroborate the notion that S100b may serve as a reliable indicator for the diagnosis of TBI during the first 24 hours after the trauma.

NFs are a kind of protein that is located in the axons and dendrites of neurons. They belong to the category of intermediate filament proteins. NFs are intermediate filament proteins found in the axons and dendrites of neurons. Gatson et al. investigated serum NF levels on the first and third days after injury to predict injury severity in patients with TBI. According to their study, patients with pathological CT findings had significantly higher NF levels than those without, and there was an inverse correlation between NF levels and GCS.[25] According to the results of the post hoc analysis performed to determine the source of the difference between the groups in the NF biomarker value in our study, it was found statistically significant that the NF biomarker level in the PICU 24-hour group was higher than that of the patients in the control and pediatric emergency groups. Still, it was lower than the patients in the PICU 48-hour group. This result shows that the NF level increases in the first 24 hours after TBI, and this level continues to increase until 48 hours. Therefore, it suggests that NF level may be an important parameter that can be used in the first 24 hours after trauma to reveal TBI and in the diagnosis and follow-up of TBI after 24 hours. This study has several notable limitations. First, as a single-center study, the sample size was limited, particularly for severe TBI cases (n=5), which restricted the generalizability of our findings. Second, the timing of sample collection posed a methodological challenge, as some blood samples were obtained more than 4 hours post-trauma, potentially missing the peak GFAP levels that typically occur within 0.5-4 hours after injury. The limited incidence of severe TBI cases restricted our capacity to thoroughly assess biomarker patterns across varying severity levels. These constraints highlight the necessity for forthcoming extensive, multi-center investigations with an equitable distribution of TBI severity cases and uniform biomarker-gathering techniques.

In conclusion, our data indicate that S-100b protein, UCHL-1, and NF are significant biomarkers for evaluating TBI severity. Each biomarker exhibits a unique temporal profile: UCHL-1 and S-100b reach their peak during the initial 24 hours post-TBI, whereas NF peaks on the second day. UCHL-1 is significantly important, exhibiting strong correlations with both CT results and patient outcomes. The inverse correlation between UCHL-1 levels and GOS-E scores suggests its potential as a predictive biomarker. These biomarkers, especially UCHL-1, may reduce reliance on repeated CT scans and facilitate earlier diagnosis and improved monitoring of TBI patients.

Ethical approval

This study has been approved by the Mersin University Ethics Committee (approval date November 7, 2018, number 2018/452). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: NNÇ, AEA; data collection: NNÇ, AK, BT, ÇE; analysis and interpretation of results: NNÇ, AEA, MA, BT, MBYÇ, AK; draft manuscript preparation: NNÇ, AEA, MA, MBYÇ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

This study was financed by the Scientific Research Projects Coordination Unit of Mersin University, under project number 2019/-1-TP3-3347.

Conflict of interest

The authors declare that there is no conflict of interest.

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