Journal of Basic Research in Medical Sciences

Journal HomePage : https://jbrms.medilam.ac.ir

Ilam University of Medical Sciences Publications

Clinical Utility of Serum Opalin in Traumatic Brain Injury

Saba Farhadian [1], **Ali Noori-Zadeh** [1]✉, **Ali Seidkhani-Nahal** [1], **Masoud Hatefi** [2]

[1] Department of Clinical Biochemistry, Faculty of Medicine, Ilam University Medical Sciences, Ilam, Iran
[2] Department of Neurosurgery, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

Article Info

Article type:
Original Article

Article History:
Received: Sep. 17, 2025
Revised: Nov. 19, 2025
Accepted: Dec. 22, 2025
Published Online: Jan. 04, 2026

✉ ***Correspondence to:***
Ali Noori-Zadeh
Department of Clinical Biochemistry, Faculty of Medicine, Ilam University Medical Sciences, Ilam, Iran

Email:
noorizadeh-a@medilam.ac.ir

A B S T R A C T

Introduction: Despite traumatic brain injury (TBI) being a leading cause of global morbidity and mortality, it lacks easy-to-access or portable, reliable biomarkers for early diagnosis. This study was designed to evaluate serum Opalin, a CNS-specific protein, in drug-naïve TBI patients.

Materials & Methods: Conducted as a prospective case-control study at a tertiary care setting, 60 drug-naïve TBI patients and 60 healthy controls (HC) were evaluated for serum Opalin levels.

Results: TBI patients showed significant alterations in serum Opalin levels. Opalin demonstrated high diagnostic accuracy (AUC: 0.943) with 86.67% sensitivity and 95% specificity at a cut-off of 321.7 pg/mL. Strong correlations were found between Opalin levels and TBI severity (using CT scan and Glasgow coma scale score).

Conclusion: This research underscores the potential application of serum Opalin to augment current evaluation methods like CT scan and Glasgow coma scale evaluations.

Keywords: Traumatic Brain Injury (TBI), Serum, Opalin, Biomarkers, Diagnosis

➢ **Cite this paper**
Farhadian S, Noori-Zadeh A, Seidkhani-Nahal A, Hatefi M. Clinical Utility of Serum Opalin in Traumatic Brain Injury. *J Bas Res Med Sci*. 2026; 13(1):100-109.

Publisher: Ilam University of Medical Sciences

Introduction

Traumatic brain injury (TBI) is a leading cause of global morbidity and mortality, ranging from mild concussions to severe brain damage due to extrinsic forces to the brain (1). The diagnosis of TBI primarily relies on clinical evaluation and neuroimaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI). However, these modalities have inherent limitations, particularly in mild TBI, where imaging often fails to detect structural changes despite significant neurological deficits. Consequently, there is increasing interest in identifying biomarkers that can serve as reliable diagnostic adjuncts to neuroimaging, enabling early diagnosis, severity stratification, and prognostication (2). Serum biomarkers are attractive due to their noninvasive nature, rapid detection, and cost-effectiveness. Recent studies have highlighted the potential of biomarkers in improving TBI diagnosis and prognosis, as seen in research on S100 calcium-binding protein B (S100B), ubiquitin C-terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP) (3). Unfortunately, the overall quality of evidence regarding the diagnostic accuracy of a single biomarker to rule out significant intracranial injury seen on CT head scans in patients with TBI is low (4). Moreover, challenges remain in translating GFAP and S100B findings from bench to bedside (5). Thus, this field merits further investigation. One promising candidate is Opalin, a myelin-associated glycoprotein predominantly expressed in the central nervous system (CNS) (6-8). Given its role in maintaining myelin integrity and potential involvement in the neuroinflammatory cascade, Opalin is emerging as a diagnostic marker that may reflect ongoing neuronal damage and axonal dysfunction in TBI. In addition to Opalin, several biochemical markers have been identified as indicators of TBI severity and clinical outcome. This study aims to evaluate the clinical utility of serum Opalin in the acute phase of TBI to evaluate its diagnostic value relative to current methods such as CT scans and the Glasgow Coma Scale (GCS).

Materials and methods

Study Design

A prospective case-control study was conducted in the Department of Neurology at Imam Khomeini Hospital, affiliated with Ilam University of Medical Sciences, over one year from 2023 to 2024.

Setting and Participants

Using a census method, a total of 91 patients diagnosed with TBI were initially recruited for this study. The diagnosis of TBI was conducted by expert neurologists based on clinical and paraclinical findings. Participants were included if they met the following criteria: a confirmed diagnosis of TBI supported by neurological examinations and CT imaging. The exclusion criteria were as follows: use of medications that affect the CNS and peripheral nervous system within the six months preceding the study (the patients must be drug-naive), any previous head injury in the past (at least 10 years ago) and presence of comorbid conditions such as neoplasms or systemic diseases. After applying these criteria, 60 drug-naive patients with TBI were selected for further analyses.

The severity of TBI (Table 1) was ordinally sub-grouped according to GCS scores as follows: HC or non-TBI (n=60, 100%): 15, mild TBI: 13-15 (n=29, 48.3%), moderate TBI: 9-12 (n=6, 10.0%), and severe TBI: 8 or lower (n=25, 41.7%). The distribution of patients according to CT scan was categorized into 7 subgroups (Table 1), including contusion/coup and countercoup (n=9, 15.0%), diffuse axonal injury (n=5, 8.3%), epidural hematoma (n=14, 23.3%), subdural hematoma (n=15, 25.0%), subarachnoid hemorrhage (n=6, 10.0%), intracerebral hemorrhage (n=8, 13.3%) and intraventricular hemorrhage (n=3, 5.0%).

There were no significant ($p > 0.05$) differences between the two groups in terms of age and sex, indicating successful matching. However, there were significant differences between the two groups in

terms of GCS score and GCS categorization (Median: 12.00 and 25-75 percentiles: 5.00 to 14.00). In the HC group (males: n= 45, 75.0% and females: n=15, 25.0%, mean age ± SD: 37.65 ± 10.30 was matched to the TBI group (males: n= 52, 86.7% % and females: n=8, 13.3%, mean age ± SD: 36.47 ± 19.18) by age (P-value= 0.6745) and sex (P-value=0.1059) to ensure comparability.

Sample Size

Using a census method, a total of 91 patients diagnosed with TBI were initially recruited for this study.

Measurements & Validity and Reliability

Demographic and Clinical Characteristics

The severity of TBI (Table 1) was ordinally sub-grouped according to GCS scores as follows: HC or non-TBI (n=60, 100%): 15, mild TBI: 13-15 (n=29, 48.3%), moderate TBI: 9-12 (n=6, 10.0%), and severe TBI: 8 or lower (n=25, 41.7%). The distribution of patients according to CT scan was categorized into 7 subgroups (Table 1), including contusion/coup and countercoup (n=9, 15.0%), diffuse axonal injury (n=5, 8.3%), epidural hematoma (n=14, 23.3%), subdural hematoma (n=15, 25.0%), subarachnoid hemorrhage (n=6, 10.0%), intracerebral hemorrhage (n=8, 13.3%) and intraventricular hemorrhage (n=3, 5.0%).

Serum Opalin Measurement

To quantitatively evaluate serum Opalin levels in both TBI and HC groups, a commercial quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit (My Biosource, Cat. No. MBS1603888) with high analytical sensitivity and specificity was used. The analytical sensitivity of the kit for detecting human Opalin was 9.89 ng/L, with a detection range of 20 ng/L to 3800 ng/L and included six calibrators (0 ng/L, 125 ng/L, 250 ng/L, 500 ng/L, 1000 ng/L, and 2000 ng/L) to establish a standard curve for quantitative analysis. Regarding analytical specificity, the manufacturer reported no significant cross-reactivity or interference between human Opalin and its analogs, ensuring reliable measurements. All procedures were carried out in strict accordance with the protocol provided by the manufacturer to ensure accuracy and reproducibility of the results.

The clinical sensitivity and specificity for various cut-off values of serum Opalin and positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were determined using MedCalc® Statistical Software (version 23.0.9). This analysis aimed to comprehensively evaluate the diagnostic performance of serum Opalin for differentiating between TBI and HC groups, thereby providing insights for its possible future clinical applicability..

Statistical and Data Analysis

Data processing, analysis and presenting the results as tables were performed using MedCalc® Statistical Software (version 23.0.9) for comparing serum biochemical analytes in both groups using a parametric unpaired t-test (independent t-test)/non-parametric Mann-Whitney test according to data distributions. The results were considered statistically significant if the P-value of the statistical test was <0.05. To determine the type of each correlation, non-parametric Spearman or parametric Pearson's correlation coefficients and their corresponding P-values were calculated and reported according to the distribution of data. Values of correlations were interpreted as 0= no correlation, 0.01-0.25= weak correlation, 0.26-0.50= sufficient correlation, 0.51-0.75= strong correlation, 0.76-0.99= very strong correlation, and 1= prefect correlation (9).

Results

Correlations Among Serum Opalin with TBI Severity

The results for correlations (correlation coefficient/r, P-value) for serum Opalin have been calculated.

Significant correlations were observed between GCS with Opalin (r=-0.918, P<0.0001) in the patients.

Subgroup Analyses Results

By non-parametric methods (subgrouping of each variable according to its reference interval), the frequency tables for each measurand and the associated chi-squared P-value have been calculated and presented in Table 1. On one hand, subgroup analyses showed that there were no statistical differences between TBI and HC using chi-squared statistical test for gender (P = 0.1059) subgroups. On another hand, there were statistical differences between TBI and HC using chi-squared statistical test for GCS (P < 0.0001, HC vs TBI: no TBI = 60 (100.0%) vs no case(0.0%), mild TBI = no case (0.0%) vs 29 (48.3%), moderate TBI = no case (0.0%) vs 6 (10.0%), severe TBI = no case (0.0%) vs 25 (41.7%),; TBI subtype (P < 0.0001, HC vs TBI: no injury 60 (100.0%) vs 0 (0.0%), contusion no case (0.0%) vs 9 (15.0%), diffuse axonal injury no case (0.0%) vs 5 (8.3%), epidural hematoma no case (0.0%) vs 14 (23.3%), subdural hematoma no case (0.0%) vs 15 (25.0%), subarachnoid hemorrhage no case (0.0%) vs 6 (10.0%), intracerebral hemorrhage no case (0.0%) vs 8 (13.3%), intraventricular hemorrhage no case (0.0%) vs 3 (5.0%).

Table 1. Subgroup analyses for gender, GCS and TBI subtypes.

A)

Group	Gender		Total
	Male	Female	
HC	45 (75.0%)	15 (25.0%)	60 (50.0%)
TBI	52 (86.7%)	8 (13.3%)	60 (50.0%)
Chi-squared	2.614		
Significance level	P = 0.1059		

B)

Group	GCS subgroup				Total
	No TBI	Mild TBI	Moderate TBI	Severe TBI	
HC	60 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	60 (50.0%)
TBI	0 (0.0%)	29 (48.3%)	6 (10.0%)	25 (41.7%)	60 (50.0%)
Chi-squared	120.000				
Significance level	P < 0.0001				

C)

Group	TBI subtype								Total
	No injury	Contusion	Diffuse axonal injury	Epidural hematoma	Subdural hematoma	Subarachnoid hemorrhage	Intracerebral hemorrhage	Intraventricular hemorrhage	
HC	60 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%	60 (50.0%)
TBI	0 (0.0%)	9 (15.0%)	5 (8.3%)	14 (23.3%)	15 (25.0%)	6 (10.0%)	8 (13.3%)	3 (5.0%)	60 (50.0%)
Chi-squared	120.000								
Significance level	P < 0.0001								

linical Utility of Serum Opalin in HC and TBI Groups

In the serum samples, Opalin protein was detectable in both HC and TBI subjects. The mean (pg/mL) ± SD in the HC and TBI groups were 165.89 ± 138.27 and 1963.45 ± 2074.65 (P<0.0001), respectively, and were presented in Table 2 and Table 3.

Table 2. Summary statistics table for HC and TBI groups.

Test/variable (unit)	Group					
	HC (n=60)			TBI (n=60)		
	Mean	95% CI	SD	Mean	95% CI	SD
Age (year)	37.650	34.989 to 40.311	10.3003	36.467	31.512 to 41.422	19.1811
Opalin (ng/L)	165.889	130.172 to 201.607	138.2662	1963.448	1427.508 to 2499.388	2074.6538
Time (minute)	0.000	0.000 to 0.000	0.0000	1025.167	750.946 to 1299.388	1061.5247
GCS	15.000	15.000 to 15.000	0.0000	9.767	8.563 to 10.970	4.6591

Abbreviations: Time: Time after traumatic brain injury; GCS: Glasgow coma scale; HC: Healthy control; TBI: Traumatic brain injury.

Table 3. Comparison of independent samples in HC and TBI groups.

Test/variable(unit)	HC (n = 60)	TBI (n = 60)	P-Value #
Age (year)	35.00 24.00 to 57.00	36.00 11.00 to 72.00	0.5281
Opalin (ng/L)	109.35 56.55 to 503.05	614.25 163.45 to 5844.10	<0.0001
GCS	15.00 15.00 to 15.00	12.00 3.00 to 15.00	<0.0001
Time (minute)	0.00 0.00 to 0.00	600.00 40.00 to 3030.00	<0.0001

Data are: Median, 5-95 percentiles

Mann-Whitney test

Abbreviations: HC: Healthy control; TBI: Traumatic brain injury; Time: Time after traumatic brain injury; GCS: Glasgow coma scale.

Moreover, receiver operating curve (ROC) was developed for serum opalin clinical sensitivity and specificity at different cut-off points, and the results have been shown in Figure 1. For a cut-off value of >321.7 pg/mL, the serum Opalin clinical utility calculated as the area under the curve (AUC) of 0.943 (95% confidence interval: 0.886 to 0.977) with a clinical sensitivity and specificity of 86.67 % (95% confidence interval: 75.4 - 94.1) and 95.00% (95% confidence interval: 86.1 - 99.0) respectively; with a Youden index J of 0.8167.

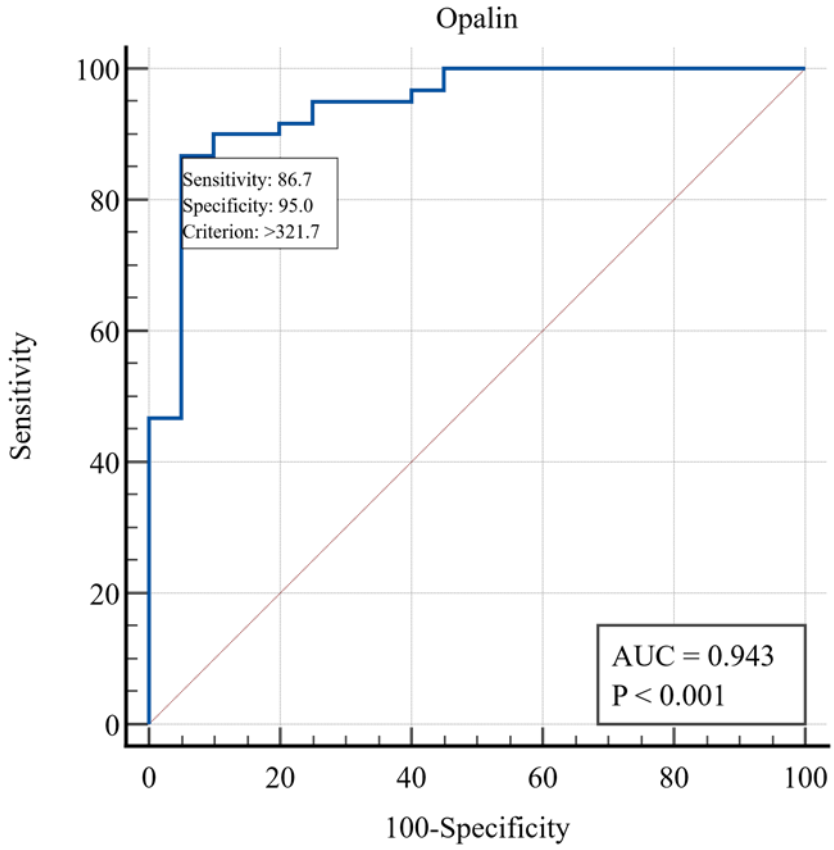

Figure 1. Receiver operating curve (ROC) for TBI diagnosis using serum opalin concentrations. For a cut-off value of >321.7 pg/mL, the serum Opalin clinical utility calculated as the area under the curve (AUC) of 0.943 (95% confidence interval: 0.886 to 0.977) with a clinical sensitivity and specificity of 86.67 % (95% confidence interval: 75.4 - 94.1) and 95.00% (95% confidence interval: 86.1 - 99.0) respectively; with a Youden index J of 0.8167.

Likelihood ratio (LR+) and negative likelihood ratio (LR-)

Meanwhile, LR+ and LR- of serum opalin were determined for the cut-off point of 321.7 pg/mL as 17.33 (95%confidence interval: 5.73 - 52.46) and 0.14 (95%confidence interval: 0.073 - 0.27

Discussion

In the current study, the serum concentration of Opalin protein was measured during the acute phase of the disease in comparison with the HC group to evaluate its diagnostic proficiency. It is well established that in TBI subjects biochemical alterations occur, even though there are many inconsistencies about the direction of the abnormalities (10, 11). The pathophysiology of TBI (induced by acute mechanical forces) involves a complex interaction between primary injury, including the immediate damage to neurons and neuroglial cells, and secondary injury, which includes a cascade of molecular and biochemical events such as inflammation, oxidative stress, and excitotoxicity. These processes lead to ischemia,

intracranial hypertension, vasogenic and cytotoxic edema, diffuse axonal injury, and hemorrhage, which contribute to neuronal death and long-term cognitive and functional impairments (12, 13). As TBI often disrupts the blood-brain barrier, leading to the leakage of proteins and other molecules from circulation into the brain and vice versa (14). In this investigation, the measurements were taken at inconsistent time points, i.e., phlebotomies were done at admissions, which could dilute any potential correlations. Serum Opalin demonstrated a very strong negative correlation with TBI severity (GCS). On one hand, it is well established that radiologic methods are the gold standard for diagnosing TBI and determining the anatomical location of the injury at admission. However, the main disadvantage associated with X-ray radiation (as used in CT scans) is the use of wavelengths ranging from 0.01 to 10 nanometers (frequencies in the range of 30 petahertz to 30 exahertz), with energies in the range of 100 eV to 100 keV (15), which are more powerful than ultraviolet (UV) radiation. Thus, it may be associated with adverse outcomes such as induction of DNA mutagenesis. This phenomenon limits the application of X-ray radiation-dependent instruments for TBI diagnosis in pregnant women and children (3). Moreover, besides safety advantages, using MRI has its limitations for the detection and monitoring of TBI, especially when the patient is under oxygen therapy or tracheostomized or in more serious conditions, such as patients with coma/unconsciousness in intensive care units. Furthermore, CT scan and MRI methods are not accessible for all patients and are limited to specific places such as hospitals or clinics. Thus, discovering an appropriate serum-based biomarker has high gains, including remote and portable examination; improving subject stratification by the extent and injury severity; detecting micro-injuries to the brain that are not monitored or detected by CT scan or MRI; advancing assessment of intoxicated, unconscious, sedated, or polytrauma patients; and identifying patients at risk of developing long-term sequelae. For several decades, researchers have conducted a growing body of investigations on cellular and biochemical markers for TBI diagnosis and have introduced many blood-based biomarkers, including astrocyte-derived proteins such as S100B (16, 17) and GFAP (18, 19) and neuron-derived proteins such as UCH-L1 (19, 20). These biomarkers have shown promise in aiding the diagnosis and understanding of TBI pathophysiology. Serum Opalin is a protein that in humans is encoded by the OPALIN gene and is a novel type I transmembrane protein enriched in differentiating oligodendrocytes (21). Indeed, Opalin is a CNS-specific myelin protein phylogenetically unique to mammals, and this specific pattern of expression makes it an appropriate candidate for TBI diagnosis (22). Moreover, in the current study, there was a very strong inverse correlation between Oplain concentrations and GCS scoring in the patients, emphasizing that it may be a serum-based biomarker for stratifying the TBI severity. A major confounding factor for the interpretation of blood-based biomarkers designed for TBI-related pathology diagnosis is that most biomarkers are expressed outside the CNS tissues to varying degrees. Thus, a pivotal issue when dealing with biomarkers is the origin of the biomarker itself, i.e., the tissue specificity of the biomarker, and interestingly, Opalin is a CNS tissue-specific protein. Unfortunately, other biomarkers such as S100B are expressed in non-specific tissues, including the breast, skin, bone marrow, adrenal gland, adipocytes, and peripheral neurons. As in polytrauma, tissue specificity of the biomarker plays a pivotal role in considering a biomarker candidate. Moreover, it is notable that S100B is expressed in the peripheral nervous system; however, as mentioned, Opalin protein is CNS-specific. Although other reported biomarkers have moderate to high clinical sensitivity or specificity for a predefined specific cut-off, in most of them, both high clinical sensitivity and specificity have not been simultaneously met (23-25). To the best of our knowledge, in contrast to their high clinical sensitivity, GFAP, S100B, and neurofilament light chain (NfL) have low clinical specificity for a specified optimal cut-off (4). Notably, it was reported

that S100B is elevated even when brain damage is not present (5, 26, 27) and GFAP is released into the bloodstream in diseases other than TBI, such as Alzheimer's disease (28). It was then shown that families of soluble protein biomarkers are indicators of blood-brain barrier disruption rather than brain damage (29, 30). These findings emphasize the importance of understanding biomarker clearance mechanisms in relation to blood-brain barrier integrity for accurate diagnostic applications. Moreover, in accordance with our study, serum Opalin was prospectively measured in a small number of TBI patients in a preliminary study, as well as in stroke patients (21, 31, 32).

Conclusion

TIn conclusion, these findings suggest that Opalin may be considered as a diagnostic biomarker for CNS injuries. However, the current investigation was conducted as a pilot study; here, we propose to investigate opalin's applicability as a TBI biomarker in larger-scale populations. This research underscores the potential use of serum Opalin that augment current evaluation methods like CT scan and GCS evaluations.

Acknowledgements

There are no acknowledgements for this article.

Ethical Considerations

EtThe study protocol was reviewed and approved by the Ethics Committee of Ilam University of Medical Sciences (IR.MEDILAM.REC.1398.033). It was conducted in full compliance with the principles outlined in the Declaration of Helsinki and adhered to the ethical standards established by the Ethics Committee of Ilam University of Medical Sciences. Written informed consent was obtained from all participants (mild severity) or the patient’s attendant TBI group before blood sample collection.

Financial Disclosure

This study was supported by a grant from Ilam University of Medical Sciences.

Conflict of interest

The author declares that there is no conflict of interest.

Authors’ contributions

Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources: SF, ANZ, Software, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: ANZ, ASN, MH.

Writing Disclosure

No writing AI assistance was utilized in the production of this manuscript.

Data Availability Statement

All data and material are available for sharing if needed with the corresponding author.

References

1. Sarkis GA, Zhu T, Yang Z, Li X, Shi Y, Rubenstein R, et al. Characterization and standardization of multiassay platforms for four commonly studied traumatic brain injury protein biomarkers: a TBI Endpoints Development Study. Biomarkers in medicine. 2021;15(18):1721-32. doi: https://doi.org/10.2217/bmm-2021-0284.
2. Tsakiris C, Siempis T, Lianos GD, Vlachodimitropoulou L, Voulgaris S, Alexiou GA. Blood biomarkers: a new solution to the silent pandemic of traumatic brain injury. Biomarkers in medicine. 2023;17(19):783-5. doi: https://doi.org/10.2217/bmm-2023-0444.
3. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol. 2022;21(11):1004-60. doi: https://doi.org/10.1016/s1474-4422(22)00309-x.
4. Rogan A, O'Sullivan MB, Holley A, McQuade D, Larsen P. Can serum biomarkers be used to rule out significant intracranial pathology in emergency department patients with mild traumatic brain injury? A Systemic Review & Meta-Analysis. Injury. 2022;53(2):259-71. doi: https://doi.org/10.1016/j.injury.2021.10.015.
5. Janigro D, Mondello S, Posti JP, Unden J. GFAP and S100B: What You Always Wanted to Know and Never Dared to Ask. Front Neurol. 2022;13:835597. doi: https://doi.org/10.3389/fneur.2022.835597.
6. Yoshikawa F, Sato Y, Tohyama K, Akagi T, Hashikawa T, Nagakura-Takagi Y, et al. Opalin, a transmembrane sialylglycoprotein located in the central nervous system myelin paranodal loop membrane. J Biol Chem. 2008;283(30):20830-40. doi: https://doi.org/10.1074/jbc.M801314200.
7. Yoshikawa F, Sato Y, Tohyama K, Akagi T, Furuse T, Sadakata T, et al. Mammalian-Specific Central Myelin Protein Opalin Is Redundant for Normal Myelination: Structural and Behavioral Assessments. PLoS One. 2016;11(11):e0166732. doi: https://doi.org/10.1371/journal.pone.0166732.
8. Kippert A, Trajkovic K, Fitzner D, Opitz L, Simons M. Identification of Tmem10/Opalin as a novel marker for oligodendrocytes using gene expression profiling. BMC Neurosci. 2008;9:40. doi: https://doi.org/10.1186/1471-2202-9-40.
9. Atee M, Hoti K, Hughes JD. Psychometric evaluation of the electronic pain assessment tool: an innovative instrument for individuals with moderate-to-severe dementia. Dementia and Geriatric Cognitive Disorders. 2018;44(5-6):256-67. doi: https://doi.org/10.1159/000485377.
10. Posti JP, Tenovuo O. Blood-based biomarkers and traumatic brain injury—A clinical perspective. Acta Neurologica Scandinavica. 2022;146(4):389-99. doi: https://doi.org/10.1111/ane.13620.
11. Gan ZS, Stein SC, Swanson R, Guan S, Garcia L, Mehta D, et al. Blood Biomarkers for Traumatic Brain Injury: A Quantitative Assessment of Diagnostic and Prognostic Accuracy. Frontiers in Neurology. 2019;10. doi: https://doi.org/10.3389/fneur.2019.00446.
12. Borgens RB, Liu-Snyder P. Understanding Secondary Injury. The Quarterly Review of Biology. 2012;87(2):89-127. doi: https://doi.org/10.1086/665457.
13. Thapa K, Khan H, Singh TG, Kaur A. Traumatic Brain Injury: Mechanistic Insight on Pathophysiology and Potential Therapeutic Targets. Journal of Molecular Neuroscience. 2021;71(9):1725-42. doi: https://doi.org/10.1007/s12031-021-01841-7.
14. Alluri H, Wiggins-Dohlvik K, Davis ML, Huang JH, Tharakan B. Blood–brain barrier dysfunction following traumatic brain injury. Metabolic Brain Disease. 2015;30(5):1093-104. doi: https://doi.org/10.1007/s11011-015-9651-7.
15. Dutta T, Santra S, Majumdar D, Mandal S. An applicative substantiation of the Radon Transform appertain to Image Segmentation for the Prognosis of Metastatic Oncogenesis vis-a-vis Lung Cancer: a Boon in the Novel Emergences of Artificial Intelligence Manoeuvred Amelioration. International Journal of Information Technology, Research and Applications. 2024;3(1):35-43. doi: https://doi.org/10.59461/ijitra.v3i1.91.
16. Santing JAL, Hopman JH, Verheul RJ, van der Naalt J, van den Brand CL, Jellema K. Clinical value of S100B in detecting intracranial injury in elderly patients with mild traumatic brain injury. Injury. 2024;55(3):111313. doi: https://doi.org/10.1016/j.injury.2024.111313.
17. Wagner R, Haider T, Babeluk R, Marhold F, Hajdu S, Antoni A. Is there a clinical benefit of S100B for the management of mild traumatic brain injury? Journal of Neurosurgery. 2025:1-7. doi: https://doi.org/10.3171/2024.10.JNS241516.
18. Michinaga S, Koyama Y. Pathophysiological responses and roles of astrocytes in traumatic brain injury. International journal of molecular sciences. 2021;22(12):6418. doi: https://doi.org/10.3390/ijms22126418.
19. Lagares A, de la Cruz J, Terrisse H, Mejan O, Pavlov V, Vermorel C, et al. An automated blood test for glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) to predict the absence of intracranial lesions on head CT in adult patients with mild traumatic brain injury: BRAINI, a multicentre observational study in Europe. eBioMedicine. 2024;110. doi: https://doi.org/10.1016/j.ebiom.2024.105477.
20. Oris C, Bouillon-Minois J-B, Kahouadji S, Pereira B, Dhaiby G, Defrance VB, et al. S100B vs. "GFAP and UCH-L1" assays in the management of mTBI patients. Clinical Chemistry and Laboratory Medicine (CCLM). 2024;62(5):891-9. doi: https://doi.org/doi:10.1515/cclm-2023-1238.
21. Silvestro S, Raffaele I, Quartarone A, Mazzon E. Innovative insights into traumatic brain injuries: biomarkers and new pharmacological targets. International Journal of Molecular Sciences. 2024;25(4):2372. doi: https://doi.org/10.3390/ijms25042372.
22. Hardt R, Jordans S, Winter D, Gieselmann V, Wang-Eckhardt L, Eckhardt M. Decreased turnover of the CNS myelin protein Opalin in a mouse model of hereditary spastic paraplegia 35. Human Molecular Genetics. 2020;29(22):3616-30. doi: https://doi.org/10.1093/hmg/ddaa246.

23. Faisal M, Vedin T, Edelhamre M, Forberg JL. Diagnostic performance of biomarker S100B and guideline adherence in routine care of mild head trauma. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2023;31(1):3. doi: https://doi.org/10.1186/s13049-022-01062-w.
24. Janigro D, Mondello S, Posti JP, Unden J. GFAP and S100B: what you always wanted to know and never dared to ask. Frontiers in neurology. 2022;13:835597. doi: https://doi.org/10.3389/fneur.2022.835597.
25. Thelin EP, Nelson DW, Bellander B-M. A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. Acta neurochirurgica. 2017;159:209-25. doi: https://doi.org/10.1007/s00701-016-3046-3.
26. Okonkwo DO, Puffer RC, Puccio AM, Yuh EL, Yue JK, Diaz-Arrastia R, et al. Point-of-care platform blood biomarker testing of glial fibrillary acidic protein versus S100 calcium-binding protein B for prediction of traumatic brain injuries: a transforming research and clinical knowledge in traumatic brain injury study. Journal of neurotrauma. 2020;37(23):2460-7. doi: https://doi.org/10.1089/neu.2020.7140.
27. Thelin EP, Zeiler FA, Ercole A, Mondello S, Büki A, Bellander B-M, et al. Serial sampling of serum protein biomarkers for monitoring human traumatic brain injury dynamics: a systematic review. Frontiers in neurology. 2017;8:300. doi: https://doi.org/10.3389/fneur.2017.00300.
28. Ozcelikay-Akyildiz G, Karadurmus L, Cetinkaya A, Uludag İ, Ozcan B, Unal MA, et al. The Evaluation of Clinical Applications for the Detection of the Alzheimer's Disease Biomarker GFAP. Crit Rev Anal Chem. 2024:1-12. doi: https://doi.org/10.1080/10408347.2024.2393874.
29. Lindblad C, Nelson DW, Zeiler FA, Ercole A, Ghatan PH, von Horn H, et al. Influence of blood–brain barrier integrity on brain protein biomarker clearance in severe traumatic brain injury: a longitudinal prospective study. Journal of Neurotrauma. 2020;37(12):1381-91. doi: https://doi.org/10.1089/neu.2019.6741.
30. Dan YR, Chiam K-H. Discovery of plasma biomarkers related to blood-brain barrier dysregulation in Alzheimer's disease. Frontiers in Bioinformatics. 2024;4:1463001. doi: https://doi.org/10.3389/fbinf.2024.1463001.
31. Kim SJ, Moon GJ, Bang OY. Biomarkers for stroke. Journal of stroke. 2013;15(1):27. doi: https://doi.org/10.5853/jos.2013.15.1.27.
32. O'Connell GC, Smothers CG, Gandhi SA. Newly-identified blood biomarkers of neurological damage are correlated with infarct volume in patients with acute ischemic stroke. Journal of Clinical Neuroscience. 2021;94:107-13. doi: https://doi.org/10.1016/j.jocn.2021.10.015.