S100B protein as a biomarker and predictor in traumatic brain injury

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Objectives. To determine the prognostic potential of S100B protein in patients with craniocerebral injury, correlation between S100B protein and time, selected internal diseases, body habitus, polytrauma, and season.
Methods. We examined the levels of S100B protein in 124 patients with traumatic brain injury (TBI).
Results. The S100B protein level 72 h after injury and changes over 72 h afterwards are statistically significant for prediction of a good clinical condition 1 month after injury. The highest sensitivity (81.4%) and specificity (83.3%) for the S100B protein value after 72 h was obtained for a cut-off value of 0.114. For the change after 72 h, that is a decrease in S100B value, the optimal cut-off is 0.730, where the sum of specificity (76.3%) and sensitivity (54.2%) is the highest, or a decrease by 0.526 at the cut-off value, where sensitivity (62.5%) and specificity (62.9%) are more balanced. The S100B values were the highest at baseline; S100B value taken 72 h after trauma negatively correlated with GCS upon discharge or transfer (r=-0.517, P<0.0001). We found no relationship between S100B protein and hypertension, diabetes mellitus, BMI, or season when the trauma occurred. Changes in values and a higher level of S100B protein were demonstrated in polytraumas with a median of 1.070 (0.042; 8.780) µg/L compared to isolated TBI with a median of 0.421 (0.042; 11.230) µg/L.
Conclusion. S100B protein level with specimen collection 72 h after trauma can be used as a complementary marker of patient prognosis.

Key words: S100B protein, traumatic brain injury, brain CT, prognosis, Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS)

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INTRODUCTION

Traumatic brain injury (TBI) remains a global problem. In adults, it is one of the leading causes of mortality and disability, and many authors refer to it as a "silent" epidemic. Following cardiovascular diseases and cancer, it is one of the leading causes of death[1]. The diagnostic gold standard in TBI is CT scan of the brain. A negative factor in the use of CT scan is the exposure to ionizing radiation, which can result in fatal malignancies[2]. These factors have led to progress in the development and availability of blood- or peripheral fluid-based biomarkers of brain injury, but in addition, they offer implications for medical decision-making and therapeutic strategies[3]. The definition of TBI biomarkers, as well as the high frequency of the association between biomarkers and TBI, is best met by the S100B protein[4].

The S100B protein is a calcium-binding protein produced primarily by astrocytes in the central nervous system[5]. Furthermore, the protein has been detected in other tissues such as bone marrow cells, chondrocytes, lymphocytes, adipocytes, and melanocytes[6]. This protein was first isolated in 1965 (ref.[7]). It is significantly involved in cell metabolism[8]. It triggers autocrine and paracrine effects in glial cells and neurons[9]. It is metabolized by the kidneys and excreted in the urine. The half-life is 30–120 minutes. The concentration of this protein after brain injury correlates with the severity and outcome of brain damage[6].

The present study sought to test the hypothesis that S100B protein can be used to predict the clinical condition of patients after TBI trauma, to determine the effect of time and to find out at the same time whether selected internal diseases, body habitus, polytrauma, and season, influence the level itself.

MATERIALS AND METHODS

Inclusion criteria for the study were graphically verified TBI, age over 18 years, and ability to collect the first specimen within 3 h of injury. All patients were subsequently admitted to hospital at the Department of Neurosurgery in Olomouc between April 2019 and December 2022. Patients under 18 years of age were not included in the study. Furthermore, patients who failed to show up for follow-up and patients with liver cirrhosis, heart attack, melanoma or other malignancy were excluded due to distorted values.

S100B protein levels were determined using peripheral blood serum collection within 3 h, then at intervals of 8,

24, and 72 h after injury. Our study is retrospective, but the time points of blood samples had to be established in advance, so there is a prospective factor.

The Glasgow Coma Scale (GCS) (ref.[10]) scoring system was used to assess the severity of injury on admission and transfer or discharge and the Glasgow Outcome Scale (GOS) (ref.[11]) upon follow-ups. Patients were invited for the follow-up approximately 1 month after the trauma.

Patients were then divided according to demographic data. The relationship of S100B protein to internal diseases was then statistically evaluated. Hypertension and diabetes mellitus were the individual variables studied. Confirmation of internal disease was based on personal medical history or relevant medication. Another variable assessed in our cohort was obesity, which was determined by body mass index (BMI). Patients with BMI value above 30 were considered obese. Patients were further divided into a group with isolated TBI and a group with polytrauma. The month of trauma was assessed and the season in which the trauma occurred was determined (spring = 3rd, 4th, 5th month, summer = 6th, 7th, 8th month, autumn = 9th, 10th, 11th month, winter = 12th, 1st, 2nd month) and the relationship to S100B protein was evaluated.

Blood specimens were processed at the local Department of Clinical Biochemistry. The S100B protein value was determined by electrochemiluminescence using the Elecsys S100 kit and Roche S100 CalSet calibrator on Cobas 8000 analyser. The reference limit (cut off) was set at the manufacturer's stated value of 0.105 μg/L.

IBM SPS Statistics for Windows, Version 23.0 statistical software was used for statistical treatment. Armonk, NY: IBM Corp. Quantitative data were described using quartiles: median (1st quartile–3rd quartile). Shapiro-Wilk test revealed that the data did not have a normal distribution. Changes in S100B protein levels over time were analysed using Friedman's test. Differences between individual pairwise times were analysed by the Wilcoxon test with Bonferroni correction. The relationship between S100B levels and the GCS and GOS scales was assessed using Spearman's correlation analysis. Mann-Whitney U test was used to assess the relationship between S100B and hypertension, diabetes mellitus, BMI, and the extent of trauma. The effect of season was tested by the Kruskal-Wallis test. Quartile box plots were used to present S100B protein levels graphically. The median level of S100B protein is demonstrated by the bold line inside the box, the bottom and top of the box represent the 1st and 3rd quartiles, and the whiskers represent the minimum and maximum S100B levels. The circle symbol indicates outliers, and the asterisk symbol indicates extreme values. The ROC (Receiver Operating Characteristic) curve was used to find the optimum cut-off value (threshold) of S100B protein level to predict favourable clinical status (GOS 4–5) 1 month after trauma. All tests were performed at the 0.05 level of statistical significance.

The study was approved by the Ethics Committee of Olomouc University Hospital.

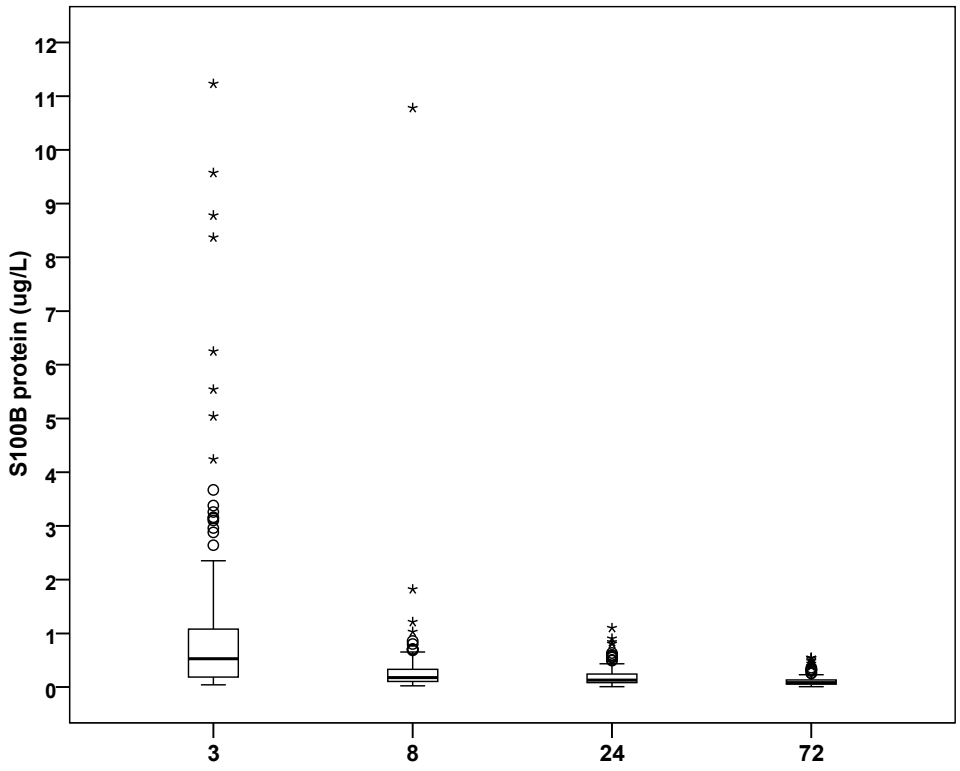

Fig. 1. Distribution of S100B protein levels over time within 3 h (3), after 8 h (8), 24 h (24) and 72 h (72).
* and ° show extreme values and outliers.

Table 1. Correlation of GCS, GCS upon discharge/transfer and GOS with S100B.

n=124		GCS	GCS upon discharge/transfer	GOS
S100B	*r*	-0.407	-0.386	0.385
within 3 h	*P*	<0.0001	<0.0001	<0.0001
S100B	*r*	-0.458	-0.465	0.428
after 8 h	*P*	<0.0001	<0.0001	<0.0001
S100B	*r*	-0.508	-0.480	0.444
after 24 h	*P*	<0.0001	<0.0001	<0.0001
S100B	*r*	-0.499	-0.517	0.425
after 72 h	*P*	<0.0001	<0.0001	<0.0001

Table 2. Results of comparison between S100B protein levels in patients with and without hypertension.

Variable	Hypertension										*P*
	Yes (n=78)					No (n=46)					
	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	
S100B within 3 h	0.634	0.042	10.280	1.371	2.012	0.435	0.052	11.230	1.248	2.313	0.291
S100B after 8 h	0.206	0.032	10.780	0.477	1.310	0.160	0.025	1.100	0.251	0.238	0.319
S100B after 24 h	0.132	0.022	1.100	0.218	0.205	0.129	0.010	0.838	0.175	0.160	0.266
S100B after 72 h	0.090	0.015	0.546	0.138	0.132	0.079	0.010	0.330	0.099	0.079	0.151
Change after 8 h	-0.290	-8.085	9.530	-0.779	2.017	-0.201	-10.821	0.061	-0.996	2.195	0.772
Change after 24 h	-0.380	-8.213	0.231	-1.019	1.669	-0.276	-11.069	0.040	-0.978	2.204	0.311
Change after 72 h	-0.481	-8.240	0.131	-1.098	1.701	-0.367	-11.178	-0.021	-1.054	2.224	0.466

Min, minimum; Max, maximum; SD, standard deviation.

Table 3. Results of comparison between S100B protein levels in treated and untreated patients with diabetes mellitus.

Variable	Diabetes Mellitus										*P*
	Yes (n=40)					No (n=84)					
	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	
S100B within 3 h	0.646	0.042	10.280	1.744	2.445	0.479	0.056	11.230	1.126	1.931	0.278
S100B after 8 h	0.234	0.025	4.380	0.377	0.699	0.164	0.030	10.780	0.399	1.181	0.670
S100B after 24 h	0.152	0.034	0.804	0.215	0.172	0.123	0.010	1.100	0.196	0.198	0.207
S100B after 72 h	0.103	0.023	0.540	0.147	0.130	0.079	0.010	0.546	0.113	0.109	0.158
Change after 8 h	-0.282	-8.085	1.700	-1.148	1.967	-0.276	-10.821	9.530	-0.726	2.127	0.534
Change after 24 h	-0.370	-8.213	0.231	-1.280	1.991	-0.339	-11.069	0.199	-0.877	1.821	0.541
Change after 72 h	-0.455	-8.240	0.131	-1.348	2.007	-0.388	-11.178	-0.021	-0.960	1.853	0.627

Min, minimum; Max, maximum; SD, standard deviation.

RESULTS

A total of 124 patients were included in the study, 36 women (29%) and 88 men (71%). The average age of the patients was 61.15 years with a range of 22 to 92 years.

Of the entire cohort, 78 patients (62.9%) were treated for hypertension and 40 patients (32.2%) for diabetes. Obesity affected 25 patients (20.2%). 33 patients (26.6%) sustained polytrauma. The most common diagnosis was acute subdural haematoma in 59 patients (47.6%), traumatic subarachnoid haemorrhage in 29 patients (23.4%), cerebral contusion in 24 patients (19.4%), epidural haematoma in 5 patients (4.0%), frontobasal trauma in 4 patients (3.2%), and intracerebral haemorrhage in 3 patients (2.4%). Of the total cohort, 5 patients died.

Assessment of the relationship between S100B protein and time of specimen collection after trauma

The highest value of S100B was recorded upon the initial/baseline sampling within 3 h – median 0.546 (0.042; 11.230) μg/L, followed by a statistically significant decrease. After 8 h, the median was 0.178 (0.025; 10.780) μg/L, $P<0.001$; after 24 h 0.130 (0.010; 1.100) μg/L, $P<0.001$ and after 72 h 0.085 (0.010; 0.546) μg/L, $P<0.001$. The distribution of S100B protein levels over time is shown in Fig. 1.

Assessment of the relationship between S100B protein and the baseline GCS, GCS on discharge/transfer, and GOS

Statistically, the GCS and GOS scales have been proven to correlate with S100B and changes in S100B. There is a negative correlation with the GCS scales – therefore, the higher the S100B, the lower the GCS and conversely. Correlations between S100B after 3, 8, 24, 72 h and GCS

Table 4. Results of comparison between S100B protein levels in patients with and without obesity based on BMI values.

Variable	BMI- Body mass index										*P*
	BMI<30 (n=40)					BMI≥30 (n=40)					
	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	
S100B within 3 h	0.531	0.052	11.230	1.303	2.123	0.633	0.042	10.280	1.413	2.148	0.903
S100B after 8 h	0.179	0.025	10.780	0.400	1.093	0.171	0.032	4.380	0.362	0.867	0.236
S100B after 24 h	0.130	0.010	1.100	0.205	0.194	0.133	0.034	0.804	0.187	0.174	0.761
S100B after 72 h	0.091	0.010	0.546	0.128	0.121	0.060	0.030	0.390	0.104	0.094	0.142
Change after 8 h	-0.275	-10.821	9.530	-0.903	2.249	-0.310	-3.049	1.700	-0.681	1.158	0.936
Change after 24 h	-0.340	-11.069	0.231	-1.055	2.026	-0.347	-3.034	0.009	-0.785	1.027	0.835
Change after 72 h	-0.390	-11.178	0.131	-1.132	2.051	-0.446	-3.064	0.009	-0.869	1.070	0.848

BMI over 30 = obesity, Min, minimum; Max, maximum; SD, standard deviation.

Table 5. Results of comparison between S100B protein levels in patients with and without polytrauma.

Variable	Polytrauma										*P*
	Yes (n=33)					No (n=91)					
	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	
S100B within 3 h	1.070	0.042	8.780	1.896	2.012	0.421	0.042	11.230	1.118	2.131	0.001**
S100B after 8 h	0.250	0.030	10.780	0.663	1.840	0.160	0.025	4.380	0.293	0.505	0.057
S100B after 24 h	0.181	0.010	0.838	0.250	0.219	0.122	0.022	1.100	0.185	0.176	0.093
S100B after 72 h	0.094	0.012	0.540	0.148	0.132	0.083	0.010	0.546	0.115	0.110	0.213
Change after 8 h	-0.653	-7.570	9.530	-1.233	2.636	-0.169	-10.821	1.700	-0.723	1.832	0.0003***
Change after 24 h	-0.726	-8.213	0.020	-1.534	1.855	-0.238	-11.069	0.231	-0.813	1.858	0.001**
Change after 72 h	-0.839	-8.240	0.006	-1.636	1.872	-0.325	-11.178	0.131	-0.883	1.885	0.0004***

Min, minimum; Max, maximum; SD, standard deviation.
Assessment of the relationship between S100B protein and season.

or GOS were moderate. The S100B value taken 72 h after sustained trauma correlated most strongly with GCS upon discharge or transfer (r=–0.517, P<0.0001). Results are shown in Table 1.

Assessment of the relationship between S100B protein and hypertension

There was no significant correlation found between S100B protein levels and hypertension. Results are shown in Table 2.

Assessment of the relationship between S100B protein and diabetes mellitus

There was no significant correlation between S100B protein levels and diabetes mellitus.

Results are shown in Table 3.

Assessment of the relationship between S100B protein and obesity according to BMI values

There was no significant correlation between S100B protein levels and obesity. The values are shown in Table 4.

Assessment of the relationship between S100B protein and polytrauma

The most common associated trauma was limb fracture (6 patients), followed by rib fracture and lung contusion (5 patients), spine fracture (5 patients), followed by combined spine and limb fractures (3 patients), followed by lung contusion (3 patients). The following associated traumas and combinations: clavicle fracture, facial skeletal fracture, vertebral and rib fracture, lung and clavicle contusion, each are represented by 2 patients. Limb fracture and chest contusion, as well as vertebral and limb fracture and lung contusion, and a combination of lung and vertebral contusion were recorded in one patient.

The occurrence of multiple traumas affected S100B levels within 3 h after injury, P=0.001. Patients with polytrauma have significantly higher S100B protein levels than patients without multiple traumas. The incidence of polytrauma also influenced the changes that occurred in 8, 24 and 72 h, where patients with polytrauma had a significantly greater decrease in S100B values. The values are shown in Table 5.

Assessment of the relationship between S100B protein and season

Out of the total, the highest number of patients with TBI trauma occurred in January (24 patients) and the lowest number in February (3 patients). Statistically, there was found no significant correlation between S100B protein levels and the season of trauma. The values are shown in Table 6.

Table 6. Results of comparing S100B protein levels in relation to season when trauma occurred.

Variable	Season												*P*
	Spring (n=29)			Summer (n=40)			Autumn (n=21)			Winter (n=34)			
	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	
S100B within 3 h	0.703	0.042	10.280	0.453	0.076	11.230	0.615	0.110	5.500	0.401	0.042	9.570	0.593
S100B after 8 h	0.275	0.030	4.380	0.162	0.032	10.780	0.162	0.051	1.100	0.163	0.025	0.707	0.546
S100B after 24 h	0.147	0.010	0.838	0.128	0.049	1.100	0.136	0.034	0.902	0.157	0.051	0.804	0.890
S100B after 72 h	0.097	0.010	0.540	0.102	0.040	0.434	0.072	0.012	0.482	0.074	0.013	0.546	0.311
Change after 8 h	-0.289	-7.570	1.700	-0.290	-10.821	9.530	-0.282	-4.575	0.061	-0.145	-9.017	0.438	0.816
Change after 24 h	-0.475	-8.213	0.040	-0.336	-11.069	0.006	-0.361	-4.805	0.199	-0.272	-9.138	0.231	0.819
Change after 72 h	-0.521	-8.240	0.009	-0.356	-11.178	-0.034	-0.428	-4.965	-0.049	-0.372	-9.243	0.131	0.878

Potential to predict good GOS based on changes in S100B protein.

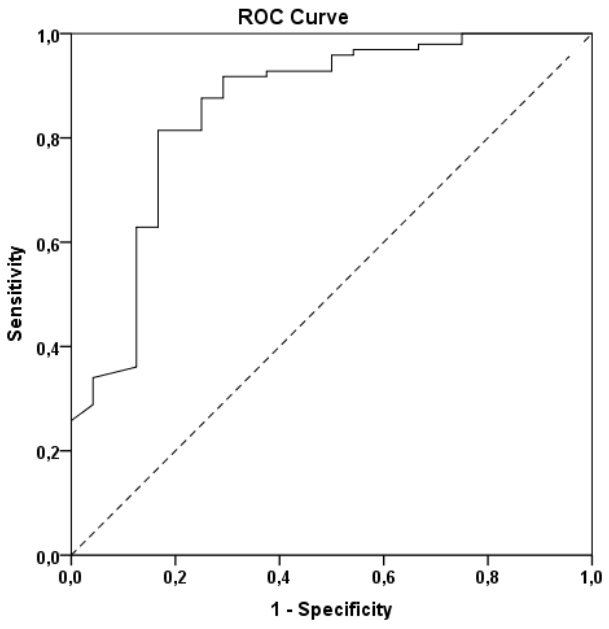

Fig. 2. ROC curve – prediction of favourable clinical condition based on the change in S100B protein levels at 72 h after trauma.
--- reference line, – change after 72 h.

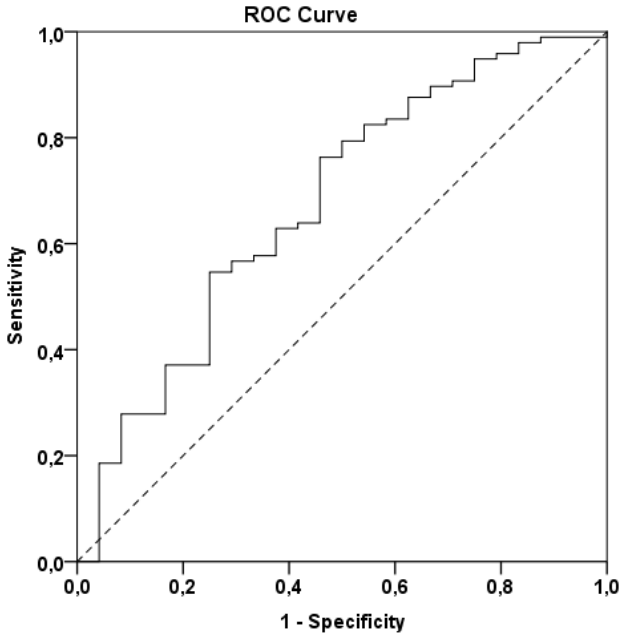

Fig. 3. ROC curve – prediction of favourable clinical status based on S100B protein level 72 h after trauma.
--- reference line, – change after 72 h.

Potential to predict good GOS based on changes in S100B protein

Out of the total of 124 patients, the clinical condition was favourable 1 month of trauma, and thus GOS 5 – good in 87 patients (70.2%) and GOS 4 – mild impairment in 10 patients (8.1%). Unfavourable clinical condition, i.e., GOS 3 was present in 12 patients (9.7%), GOS 2 – vegetative state in 10 patients (8.1%) and GOS 1 – death in 5 patients (4%).

The change after 72 h is statistically the most significant for predicting good clinical outcome. For the change after 72 h with AUC=0.675 (95% CI 0.549–0.800), *P*=0.008 – test is sufficiently discriminating (Fig. 2). For the change in S100B protein after 72 h, the optimal cut-off value is a decrease by 0.730, where the sum of specificity (76.3%) and sensitivity (54.2%) is the highest, or cut-off value decrease by 0.526 when sensitivity (62.5%) and specificity (62.9%) are more balanced.

Possibility to predict good GOS based on S100B protein values

Only the S100B protein determination 72 h after injury was statistically significant for predicting a good clinical outcome. In ROC analysis, the AUC value = 0.856 (95% CI 0.763–0.949). The test is therefore very well discriminating (Fig. 3). The highest sensitivity (81.4%) and specificity (83.3%) for predicting good GOS was obtained for a cut-off value of 0.114 for the S100B protein value in 72 h.

DISCUSSION

Our study supports the potential of using S100B protein to assess the prognosis of patients with TBI. Statistically significant for predicting good clinical condition 1 month after trauma, i.e., GOS 4 and 5, is determination of S100B protein 72 hours after trauma and then its change in 24 and 72 h after trauma. Supporting claim of the potential to use S100B protein as an indicator of injury severity and prediction of condition is also presented by Žurek et al.[12]. The prognostic value of the S100B collected 12–36 h after trauma is also supported by Thelin et al.[13].

Statistically, the highest S100B value was observed at the initial sampling within 3 h. Wijanarko et al. in their study point to changes in S100B levels in the form of decreased levels 3 h of trauma[14]. Elevated levels of S100B protein are caused by releasing from injured brain cells[15] and it is the continuous release from injured brain tissue that leads to the protein being detectable beyond the expected half-life[16].

In the cohort, we found a negative correlation between S100B protein and GCS. The strongest degree of correlation was proven for changes in S100B 72 h after trauma with GCS on discharge. A similar result of negative correlation we have described in a smaller sample of 22 patients in our earlier publication, with the strongest correlation demonstrated after 72 h (ref.[4]). S100B protein values can be used for patient stratification, low S100B protein values are observed in patients with mild traumatic brain injury[17].

Apart from the use of S100B protein as a TBI trauma biomarker, recent studies also indicate other possible applications. This protein can also be used as a predictor of hypertension[18]; however, in our cohort, no correlation between S100B protein and hypertension was proven. Current knowledge of the S100B protein and its uses is beyond the scope of this communication. Another possible use of S100B protein is as a correlate for insulin resistance/diabetes mellitus type 2 and for metabolic risk assessment[19]. One of components of the metabolic syndrome, in addition to diabetes mellitus, is obesity. Kheirouri et al. in their study of 44 patients with and without metabolic syndrome demonstrated statistically significantly elevated S100B protein levels in patients with metabolic syndrome[20]. In our study, no association between S100B protein values and obesity or diabetes mellitus was proven. In addition, our results support the results of Pham et al., who in a sample of 200 patients found no statistically relationship between BMI and levels of S100B protein[21].

Significantly higher S100B protein levels and their destruction were observed in the studied patients with polytrauma. This is due to extracranial production. In patients with polytrauma, regardless of TBI, there is an increase in values[22]. This agrees with the results of by Thelin et al., who recommended collecting the specimen 12–36 h post-trauma[13] to obviate biased values for the predictive ability of S100B protein early after trauma.

S100B has a circadian rhythm in healthy people, but its seasonal variations were addressed by Morera-Fumero et al. In their study, where they showed a significant difference in the concentration of S100B protein in summer and winter[23]. In our study, no relationship between S100B protein level and season was demonstrated in TBI patients.

Despite the known possibility of using S100B protein for its prognostic potential, the main contribution of this study is the finding that the described correlations between selected internal diseases, body habitus, season and S100B protein are not confirmed in TBI patients. Conversely, when interpreting the results of patients with polytrauma, it is important to remember that the S100B protein value is modified. A benefit that cannot be overlooked is the obtained S100B values associated with good patient prognosis, offering therapeutic advantages in addition to the prognostic ones.

The aim of the study is not to replace CT in the diagnosis of TBI, but to point out the possibility of additional diagnostic options, such as the S100B protein.

CONCLUSION

Collection of S100B protein 72 hours after trauma can be used as an additional marker of patient prognosis. The baseline value is influenced by the associated trauma. Values are not affected by hypertension, diabetes mellitus, habitus, or season when the trauma occurred.

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REFERENCES

1. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, Agrawal A, Adeleye AO, Shrime MG, Rubiano AM, Rosenfeld JV, Park KB. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018:1-18. doi: 10.3171/2017.10.JNS17352
2. Wijanarko F, Sungkar AA, Saadhi I, Setiawati DA. S100β protein levels as a parameter to assess the clinical development of adult patients with mild traumatic brain injury in Dr. Moewardi Public Hospital, Surakarta. Surg Neurol Int 2021;12:342. doi: 10.25259/SNI_294_2021
3. 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.
4. Trnka Š, Jablonský J, Stejskal P, Hrabálek L, Vaverka M, Krahulík D. Protein S100B a jeho prognostické možnosti u kraniocerebrálních traumat. Cesk Slov Neurol N 2021;84(6):562-6. (In Czech)

5. Tateishi N, Shimoda T, Yada N, Shinagawa R, Kagamiishi Y. S100B: astrocyte specific protein. Nihon Shinkei Seishin Yakurigaku Zasshi 2006;26(1):11-6. (In Japanese)
6. Rezaei O, Pakdaman H, Gharehgozli K, Simani L, Vahedian-Azimi A, Asaadi S, Sahraei Z, Hajiesmaeili M. S100 B: A new concept in neurocritical care. Iran J Neurol 2017;16(2):83-9.
7. Moore BW. A soluble protein characteristic of the nervous system. Biochem Biophys Res Commun 1965;19(6):739-44. doi: 10.1016/0006-291x(65)90320-7
8. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, Geczy CL. Functions of S100 proteins. Curr Mol Med 2013;13(1):24-57.
9. Sorci G, Riuzzi F, Arcuri C, Tubaro C, Bianchi R, Giambanco I, Donato R. S100B protein in tissue development, repair and regeneration. World J Biol Chem 2013;4(1):1-12. doi: 10.4331/wjbc.v4.i1.1
10. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2(7872):81-4.
11. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1(7905):480-4.
12. Žurek J, Bartlová L, Marek L, Fedora M. Sérový protein S100B jako molekulární marker závažnosti poranění mozku u dětí. Cesk Slov Neurol N 2010;73/106(1):37-44. (In Czech)
13. Thelin EP, Johannesson L, Nelson D, Bellander BM. S100B is an important outcome predictor in traumatic brain injury. J Neurotrauma 2013;30(7):519-28.
14. Wijanarko F, Alifianto U, Setyono H, Arsika Ramadhana G, Sungkar AA, Saadhi I, Setiawati DA. S100β protein levels as a parameter to assess the clinical development of adult patients with mild traumatic brain injury in Dr. Moewardi Public Hospital, Surakarta. Surg Neurol Int 2021;12:342. doi: 10.25259/SNI_294_2021
15. Marmarou A, Portella G, Barzo P, Signoretti S, Fatouros P, Beaumont A, Jiang T, Bullock R. Distinguishing between cellular and vasogenic edema in head injured patients with focal lesions using magnetic resonance imaging. Acta Neurochir Suppl 2000;76:349-51. doi: 10.1007/978-3-7091-6346-7_72
16. Müller K, Townend W, Biasca N, Undén J, Waterloo K, Romner B, Ingebrigtsen T. S100B serum level predicts computed tomography findings after minor head injury. J Trauma 2007;62(6):1452-6.
17. Herrmann M, Jost S, Kutz S, Ebert AD, Kratz T, Wunderlich MT, Synowitz H. Temporal profile of release of neurobiochemical markers of brain damage after traumatic brain injury is associated with intracranial pathology as demonstrated in cranial computerized tomography. J Neurotrauma 2000;17(2):113-22.
18. Sherstnev VV, Gruden' MA, Elistratova EI, Karlina VP, Kuznetsova AV, Ryzhova TV, Ryzhov VM, Sen'ko OV. Pre-Hypertension and Hypertension. Bull Exp Biol Med 2015;158, 604-6.
19. Riuzzi F, Chiappalupi S, Arcuri C, Giambanco I, Sorci G, Donato R. S100 proteins in obesity: liaisons dangereuses. Cell Mol Life Sci 2020;77(1):129-47.
20. Kheirouri S, Ebrahimi E, Alizadeh M. Association of S100B Serum Levels with Metabolic Syndrome and its Components. Acta Medica Portuguesa 2018;31(4):201-6.
21. Pham N, Fazio V, Cucullo L, Teng Q, Biberthaler P, Bazarian JJ, Janigro D. Extracranial sources of S100B do not affect serum levels. PloS One 2010;5(9):12691.
22. Pfortmueller CA, Drexel C, Krähenmann-Müller S, Leichtle AB, Fiedler GM, Lindner G, Exadaktylos AK. S-100 B Concentrations Are a Predictor of Decreased Survival in Patients with Major Trauma, Independently of Head Injury. PLoS One 2016;11(3):e0152822. doi: 10.1371/journal.pone.0152822
23. Morera-Fumero AL, Abreu-Gonzalez P, Henry-Benitez M, Yelmo-Cruz S, Diaz-Mesa E. Summer/winter changes in serum S100B protein concentration as a source of research variance. J Psychiatr Res 2013;47(6):791-5.