

Evaluation of Serum Prestin as a Potential Biomarker for Trauma Severity in Patients with Traumatic Brain Injury

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Objective : Prestin, expressed in cochlear outer hair cells, is essential for auditory signal amplification and may serve as a biomarker for cochlear injury related to trauma. This study aimed to investigate the potential role of prestin in the diagnosis and prognosis of cranial trauma.

Methods : A total of 150 participants were included, comprising 110 patients aged 18–70 who were treated for head trauma and 40 age-matched healthy controls. The patients were divided into two groups of 55 each, with Glasgow coma scale (GCS) ≥ 13 and GCS ≤ 8 , according to the GCS. Prestin was measured by enzyme-linked immunosorbent assay in serum on days 1, 3, and 7 in the patient and also the control groups. In the diagnosis of trauma and determining trauma severity, important risk levels (cut-off values) according to prestin's measurement days were calculated by receiver operating characteristic (ROC) analysis.

Results : Prestin values in both the GCS ≥ 13 and GCS ≤ 8 groups were dramatically lower than those in the control on all measurement days. Additionally, prestin values in the GCS ≤ 8 group on days 3 and 7 tended to be lower than those in the GCS ≥ 13 group. Furthermore, there was a tendency for serum prestin values to increase as time progressed especially in the GCS ≥ 13 group. ROC analysis showed that prestin values on the first, third, and seventh days showed high accuracy in detecting traumatized individuals with area under the curve (AUC) values of 85%, 81%, and 75%, respectively (sensitivity : 84%, 79%, and 83%, respectively). Also, prestin data on the first day accurately detected the severity of trauma at a high rate (sensitivity, 82%; AUC, 90%).

Conclusion : Our findings suggest that serum prestin levels on the first day after trauma may provide supportive information regarding trauma severity. However, further controlled studies are needed before definitive diagnostic or prognostic use.

Key Words : Cranial trauma · Prestin · Prognosis · Diagnosis · Trauma severity.

INTRODUCTION

Head trauma is one of the important causes of mortality and

morbidity in society⁵⁾. Life-threatening or irreversible sequelae following trauma may lead to situations requiring surgery^{16,27)}. Long intensive care follow-ups and expensive radiological ex-

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aminations after trauma can take a long time, vary depending on the physician, and cannot be fully optimized. For this reason, in order to reduce mortality or morbidity and provide early surgical intervention to patients, the investigation of new, reliable, low-cost biochemical biomarkers that can be measured quickly has become a priority in recent years to diagnose traumatic brain injury^{8,12}. It has been reported that peripheral blood analysis to identify brain-specific biomarkers in head trauma may be clinically useful in detecting developing damage¹⁵.

Glasgow coma scale (GCS) is generally used as the gold evaluation method to determine the prognosis after head trauma and to evaluate the clinical course of the patient. The prognosis is not fully known, especially in patients with loss of consciousness and those who are followed in intensive care. The lack of a biochemical marker that can be used for the clinical course other than radiological examinations in patients followed up with the GCS score seriously challenges the clinician^{23,24}. This makes it very important to investigate new biochemical biomarkers in the diagnosis and prognosis of trauma.

The cochlea may be affected after head trauma. The main function of outer hair cells is to generate mechanical force to strengthen the vibration wave in the cochlea. Prestin is a motor protein specific to the cochlea and expressed from outer hair cells^{2,13}. Decreased prestin levels may cause loss of electromotility in outer hair cells. Since prestin can cross the blood-labyrinth barrier, it can be released into the peripheral blood circulation. Prestin has primarily been studied in relation to acoustic exposure and otologic surgical trauma, and additional research is required to clarify its potential role in larger trauma populations^{3,17,32}.

In brain-specific head trauma, many biomarkers such as glial fibrillary acidic protein (GFAP), glial protein S-100 beta (S100B), neuron-specific enolase (NSE) have been investigated, and their levels in peripheral blood have been monitored^{1,8}. However, since these biomarkers can be secreted from cells outside the intracranial region of the body in multi-trauma patients without head trauma, they may give incorrect results and have low specificity¹⁵. In this study, how the levels of prestin, which is secreted only from the cochlea in the intracranial area, change in head trauma, its correlation with GCS, and its diagnostic and prognostic performance in head trauma were investigated.

MATERIALS AND METHODS

Ethical approval and study design

Ethical approval was received for this study from the Institution's Clinical Research Local Ethics Committee (decision No. 03; date : March 15). All patients and volunteers (or their legal guardians for those unable to give consent) were included in the study after informed consent was obtained. The study was conducted in a prospective observational design.

Group 1 : control

The control group consisted of 40 healthy volunteers, similar in age and gender to the patient groups. None of the volunteers had a history of neurological, metabolic, otological, or systemic disease. Routine biochemistry tests were within normal limits, and there was no history of hearing loss.

Patient groups

The study included 110 patients between the ages of 18 and 70 who were admitted to the hospital due to head trauma and were followed up in the ward or intensive care unit. The patients were divided into two groups according to the GCS : group 2, GCS $\geq$ 13 (mild head trauma) and group 3, GCS $\leq$ 8 (severe head trauma).

Exclusion criteria

Chronic systemic diseases (diabetes, thyroid, rheumatological, connective tissue diseases, etc.), chronic middle ear infection, history of acoustic trauma, or prior otologic surgery were also excluded. Additionally, patients with longitudinal or transverse temporal bone fractures, polytrauma, or concomitant craniofacial injuries were also excluded to minimize potential confounding effects on prestin levels. Additionally, there was no use of any drugs or cigarettes in both the control and patient groups.

Demographic and clinical data

For each patient, age, sex, medical history, mechanism of injury (fall, vehicle accident, assault, etc.), and concomitant extracranial injuries (thorax, abdomen, or extremity) were recorded. The type of head injury was determined by cranial computed tomography scan and classified as epidural hematoma, epidural hematoma + pneumocephalus, subdural hematoma, subdural hematoma + subarachnoid hemorrhage, or subarachnoid hem-

orrhage. Cases with multiple lesions were designated as “mixed lesions.”

Collection of blood and serum samples

Three mL of blood from each of the patients on the first, third, and seventh days of hospitalization, as well as from the volunteers in the control group on the same days, was collected in routine biochemistry tubes without anticoagulant and centrifuged at $3000\times g$ for 10 minutes. The resulting serum samples were stored at -80°C until the time of analysis.

Measurement of serum prestin levels

The prestin values in serum samples were measured at 450 nm in BioTek EL&800 device (BioTek, Winooski, VT, USA) by following the instructions in the kit procedure with commercially purchased ELISA kits (BT LAB Jiaying Korain Biotech Co. Ltd., Zhejiang, China; Cat No. E4170Hu). The obtained absorbance values were calculated quantitatively using the standard curve equation.

Statistical analysis

The normality assumption of the data was examined by Shapiro-Wilk test. Homogeneity of group variances was checked by Levene's test. The values of prestin measurements according to groups and time did not meet the assumption of normal distribution. Therefore, median and interquartile range values were given for descriptive statistics of prestin measurement values. To assess changes in prestin levels over time (days 1, 3, and 7) and differences by GCS group ($\text{GCS} \geq 13$: mild; $\text{GCS} \leq 8$: severe), linear mixed models (LMM) were used, taking into account repeated measures. First, a basic model (model 1) was constructed, including only time and group variables. Demographic (age, sex) and clinical (intracranial lesion type) covariates were then added stepwise (models 2–3). Time (days 1, 3, and 7) and group (mild and severe trauma) variables were defined as fixed effects in the model. A random intercept was added for each individual and controlled for interindividual baseline differences. Age, sex, and intracranial lesion type were added stepwise as covariates to the model : model 1, time and GCS group; model 2, model 1 + age and sex; model 3, model 2 + intracranial lesion type; model 4, model 3 + time $\times$ GCS group interaction; and model 5, model 4 + all covariates.

Extended models (models 4–5) that included an interaction term were not included in the analysis due to high variance in-

flation and model convergence issues. Correlation was included in the model as a random intercept to account for potential dependence between repeated measurements. To confirm the results obtained in the LMM independently of model assumptions, the models were also validated using Generalized Estimating Equations (GEE), and similar results were obtained. In the GEE analysis, prestin level was the dependent variable, time (1st, 3rd, 7th day) was the within-subject factor, and group (mild/severe trauma) was the between-subject factor. The correlation structure was set to Exchangeable.

Differences between repeated prestin measurements across groups over time were demonstrated in detail using Friedman's two-way analysis of variance for released samples. Differences between prestin measurement values across groups at the same time point were analyzed using the Kruskal-Wallis test. The Mann-Whitney U test with Bonferroni correction was used for multiple comparisons between subgroups. In addition, the distributions of prestin measurement values according to groups and time were summarized with box-plot graphs, and the results of multiple comparisons were shown in these graphs. Box-plot graphs were created at 95% confidence level. Receiver operating characteristic (ROC) analysis was run to determine the diagnostic and prognostic performance of prestin in the diagnosis and severity of trauma and to calculate the significant risk levels. Cut-off values were calculated with Youden index. Area under the curve (AUC) values, sensitivity, and specificity criteria were used for the diagnostic and prognostic performance of prestin. Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

Basic demographic characteristics of the patient and control groups regarding age, gender, injury mechanism, and trauma types are summarized in Table 1. The median age in the GCS groups was 39, and the quartiles were 26 and 57. In the control group, the median was 41, and the quartiles were the same as the GCS groups (25th percentile, 26; 75th percentile, 57). As a result of the analysis, no statistically significant difference was found between the groups in terms of age ($p=0.920$). This result indicates that the age distribution was similar between the GCS groups and the control group. Of the 110 participants in the

study, 86 were male (78.2%) and 24 were female (21.8%). The gender distribution was the same in the GCS >13 and GCS <8 groups. Males were 78.2% and females were 21.8% in both groups. This is also supported by the chi-square analysis finding $p=1.00$ ($p>0.05$). The analysis showed that gender was not a significant variable between the GCS groups and that the groups were balanced in terms of gender.

The most common conditions among the 110 patients in the study were “no intracranial lesion type” (36.4%) and subarachnoid hemorrhage (20.9%). Other intracranial lesion types were less common. The distribution of intracranial lesion types was quite similar in the GCS >13 and GCS <8 groups. For example, the rates of “no intracranial lesion type” and subdural hematoma were equal in both groups (36.4% and 18.2%). The chi-square test result was 0.996, indicating no significant difference

in intracranial lesion type distribution between the GCS groups ($p>0.05$). Consequently, no statistically significant difference was observed in intracranial lesion types according to GCS level.

Both the stepwise covariate addition model (Table 2; $\beta=0.45$, $p=0.002$) and the GEE analysis (Table 2; $\beta=0.47$, $p=0.002$) showed that prestin levels increased significantly over time. Prestin levels were significantly higher in the severe head trauma (GCS ≤ 8) group than in the mild trauma group (GCS ≥ 13) (Table 2; $\beta=1.05$, $p<0.001$). When variables such as age, gender, and intracranial lesion type were included in the model, no significant effect of these variables on prestin was found (all $p>0.05$). In the LMM models, adding covariates slightly increased the explanatory power of the model (R^2 : 0.41→0.44). Confirmation with the GEE analysis also yielded similar re-

Table 1. Demographic data of volunteers and percentages of intracranial lesion types in patient groups

	Gender			Intracranial lesion types						Total
	Male	Female	Total	No lesion	Epidural hematoma	Epidural hematoma + pneumo- cephalus	Subdural hematoma	Subdural hematoma + subarachnoid hemorrhage	Subarachnoid hemorrhage	
Group										
GCS >13										
Count	43	12	55	20	3	1	10	11	10	55
% within grup	78.2	21.8	100.0	36.4	5.5	1.8	18.2	20.0	18.2	100.0
% within gender	50.0	50.0	50.0							
% within intracranial lesion type				50.0	50.0	100.0	50.0	55.0	43.5	50.0
% of total	39.1	10.9	50.0	18.2	2.7	0.9	9.1	10.0	9.1	50.0
GCS <8										
Count	43	12	55	20	3	0	10	9	13	55
% within grup	78.2	21.8	100.0	36.4	5.5	0.0	18.2	16.4	23.6	100.0
% within gender	50.0	50.0	50.0							
% within intracranial lesion type				50.0	50.0	0.0	50.0	45.0	56.5	50.0
% of total	39.1	10.9	50.0	18.2	2.7	0.0	9.1	8.2	11.8	50.0
Total										
Count	86	24	110	40	6	1	20	20	23	110
% within grup	78.2	21.8	100.0	36.4	5.5	0.9	18.2	18.2	20.9	100.0
% within gender	100.0	100.0	100.0							
% within intracranial lesion type				100.0	100.0	100.0	100.0	100.0	100.0	100.0
% of total	78.2	21.8	100.0	36.4	5.5	0.9	18.2	18.2	20.9	100.0

GCS: Glasgow coma scale

sults. In the GEE analysis, the interaction between group, time, and group×time was found to be significant ($p<0.05$). Accordingly, the rate of increase in prestin was more pronounced in

the severe trauma group. Furthermore, age and other covariates remained non-significant in the GEE analysis (Table 2). The results supported the notion that trauma severity and time course

Table 2. Stepwise covariate addition model results (dependent variable : prestin level) and GEE analysis results

Variable	Stepwise covariate addition model						GEE analysis			
	Model 1 ($\beta \pm SE$)	p -value	Model 2 ($\beta \pm SE$)	p -value	Model 3 ($\beta \pm SE$)	p -value	β	Std. error	Wald chi-squared	p -value
Time	0.48±0.12	0.001	0.46±0.13	0.002	0.45±0.13	0.002	0.47	0.11	17.8	<0.001
Groups, GCS ≤8 and GCS ≥13	1.12±0.28	<0.001	1.09±0.29	<0.001	1.05±0.30	<0.001				
Group, GCS ≤8							1.09	0.26	22.1	<0.001
Time×group interaction							0.21	0.09	5.4	0.021
Age	—	—	0.01±0.01	0.31	0.01±0.01	0.34	0.01	0.01	1.0	0.31
Gender	—	—	0.07±0.09	0.42	0.06±0.09	0.48	0.07	0.09	0.6	0.44
Intracranial lesion type	—	—	—	—	0.09±0.10	0.37	0.08	0.10	0.7	0.39
Model R ²	0.41	—	0.43	—	0.44	—				

GEE : generalized estimating equations, SE : standard error of mean, Std. : standard, GCS : Glasgow coma scale

Table 3. Descriptive statistical values of prestin measurement according to groups and time

Group	First day values of prestin (pg/mL)		Third day values of prestin (pg/mL)		Seventh day values of prestin (pg/mL)		p -value*
	Median	IQR	Median	IQR	Median	IQR	
Control	783.97	1197.2	1164.47	1347.76	882.36	1346.43	0.218
GCS ≥13	234.07	106.63	397.43	1178.11	456.74	297.78	<0.001
GCS ≤8	369.34	139.92	313.97	125.07	379.39	171.47	0.312
p -value [†]	<0.001		<0.001		<0.001		

* p -values show the results of the "Friedman's two-way analysis of variance for related samples." [†] p -values indicate Kruskal-wallis analysis results. IQR : interquartile range, GCS : Glasgow coma scale

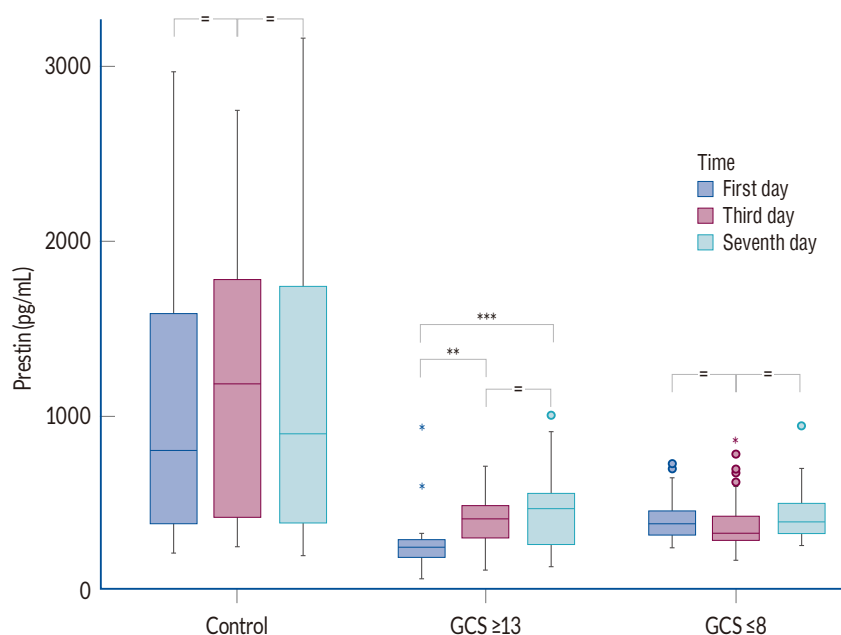


Fig. 1. Average change levels and differences in repeated prestin measurements over time for the groups. Error bars are calculated at a 95% confidence level. ** $p<0.01$ and *** $p<0.001$ were accepted as significant. GCS : Glasgow coma scale.

change are the primary determinants of prestin levels.

When Table 3 and Fig. 1 were examined, the median prestin values of the control group on the first, third and seventh days were similar to each other and there was no significant difference between them ($p>0.05$). However, in the GCS ≥ 13 group, although the median prestin values were at the lowest level on the first day, they were restored and increased on the third and seventh days ($p<0.01$). In addition, in the GCS ≥ 13 group, the increases in the median values of prestin revealed a significant difference between the first and third day values and between the first and seventh day values ($p<0.01$), while there was no significant difference at between the third day and the seventh day ($p>0.05$). In addition, in the GCS ≤ 8 group, the median levels of prestin did not change much on the first, third, and sev-

enth days and remained significantly lower than the control group values ($p<0.01$).

When Table 3 and Fig. 2 were examined, the median values of prestin on the first day were significantly different from each other in all the groups, and while these values were at the highest in the control group, they were at the lowest level in the GCS ≥ 13 group ($p<0.01$). Median values of prestin on the third day in the GCS ≥ 13 and GCS ≤ 8 groups were significantly lower than the median values of prestin in the control group on the same day ($p<0.01$). However, the median prestin values of the GCS ≥ 13 and GCS ≤ 8 groups on the third day were similar to each other and there was no significant difference between them. In addition, the median values of prestin on the seventh day in the GCS ≥ 13 and GCS ≤ 8 groups were significantly de-

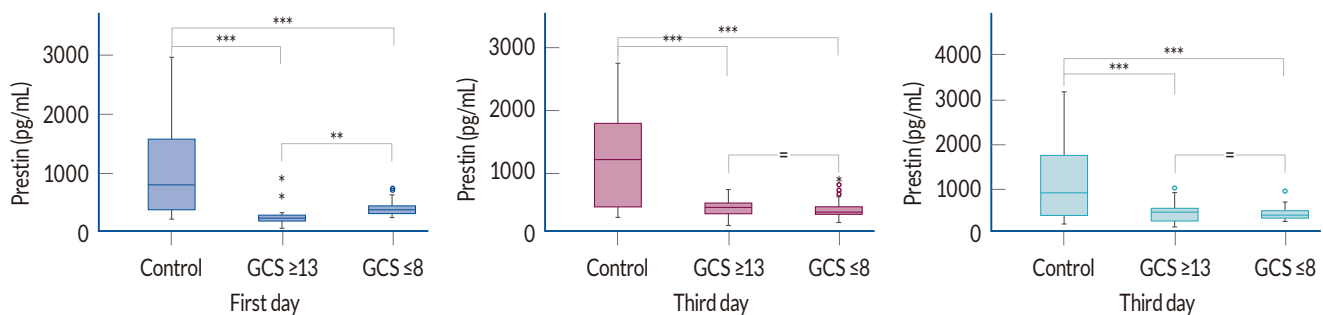


Fig. 2. Average change levels and differences in prestin measurements between groups within the same time period. Error bars are calculated at a 95% confidence level. ** $p<0.01$ and *** $p<0.001$ was accepted as significant. GCS : Glasgow coma scale.

Table 4. Diagnostic performance results of prestin levels in trauma diagnosis according to measurement days and performance results of prestin levels in detecting severe and mild trauma (prognosis) according to measurement days

	Cut-off value (pg/mL)	AUC (%) (95% CI)	Std. error	Asymptotic Sig.	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Diagnostic performance results of prestin levels in trauma diagnosis according to measurement days						
Prestin measurement day						
First day	<415.77	0.85 (0.77-0.92)	0.038	<0.001	0.84 (0.81-0.87)	0.73 (0.69-0.77)
Third day	<472.71	0.81 (0.73-0.90)	0.044	<0.001	0.79 (0.72-0.83)	0.70 (0.68-0.74)
Seventh day	<548.11	0.75 (0.65-0.86)	0.053	<0.001	0.83 (0.77-0.85)	0.63 (0.61-0.69)
Performance results of prestin levels in detecting severe and mild trauma (prognosis) according to measurement days						
Prestin's measurement day						
First day	>293.29	0.90 (0.84-0.96)	0.031	<0.001	0.82 (0.79-0.86)	0.84 (0.82-0.87)
Third day	<392.94	0.57 (0.47-0.69)	0.056	<0.001	0.71 (0.67-0.74)	0.55 (0.51-0.56)
Seventh day	<405.98	0.51 (0.40-0.63)	0.058	<0.001	0.62 (0.56-0.65)	0.58 (0.55-0.61)

AUC : area under the curve, CI : confidence interval, Std. : standard, Sig. : significance

creased compared to the control group ($p < 0.01$). In addition, although the median values of prestin on the seventh day in the $GCS \leq 8$ group were lower than in the $GCS \geq 13$ group, there was no significant difference between them ($p > 0.05$). To determine head trauma, significant risk levels (cut-off values) of prestin according to measurement days were calculated by running ROC analysis, and findings regarding the diagnostic performance of prestin were obtained according to these values (Table 4 and Fig. 3A). Considering the cut-off values of prestin according to the measurement days, it was seen that the prestin values on the first, third, and seventh days accurately detected the traumatized individuals with AUC values of 85%, 81%, and 75%, respectively (high sensitivity : 84%, 79%, and 83%, respectively). However, prestin levels on the third and seventh days were found to be less successful (lower specificity) than the first day in detecting individuals who did not experience trauma. Moreover, considering Prestin's cut-off value on day 1, it was observed that a large proportion (AUC, 85%) of patients who were predicted to have experienced trauma, actually experienced trauma. In addition, the high AUC value (0.85) of prestin values on the first day showed that the false prediction rate of this biomarker in determining the diagnosis of trauma was quite low. Accordingly, prestin values less than 415.77 pg/mL, especially measured on the first day, were found to be a significant risk level for the diagnosis of trauma.

In determining the severity (prognosis) of trauma, significant risk levels (cut-off values) of prestin according to measurement days were calculated by running ROC analysis, and findings regarding the prognostic performance of prestin were

obtained according to these values (Table 4 and Fig. 3B). Considering the cut-off values of prestin according to measurement days, it was seen that the prestin values on the first day accurately detected the severity of trauma at a high rate (sensitivity, 82%; AUC, 90%). Additionally, prestin values on the first day largely correctly identified patients with mild trauma (specificity, 84%). However, prestin levels on the third and seventh days were found to be unsuccessful compared to the first day prestin values in determining severe trauma (specificity and AUC values 71% and 57%, and 62% and 51%, respectively). Moreover, considering Prestin's cut-off value on day 1, it was observed that a large proportion of patients (AUC, 90%) who were predicted to have experienced severe trauma, actually experienced severe trauma. In addition, the high AUC value of prestin values on the first day revealed that the false prediction rate of this biomarker in the detection of severe trauma was quite low (specificity, 84%).

DISCUSSION

It is important to determine the prognosis of head trauma in order to organize appropriate treatment and evaluate clinical progression. To determine the prognosis, clinical evaluations, laboratory tests, electrophysiological tests, and radiological images are used²⁸. GCS, defined in 1974, is the most important and gold parameter used today to determine the severity of head trauma. However, since GCS is thought to be insufficient in determining prognosis, new biochemical parameters that

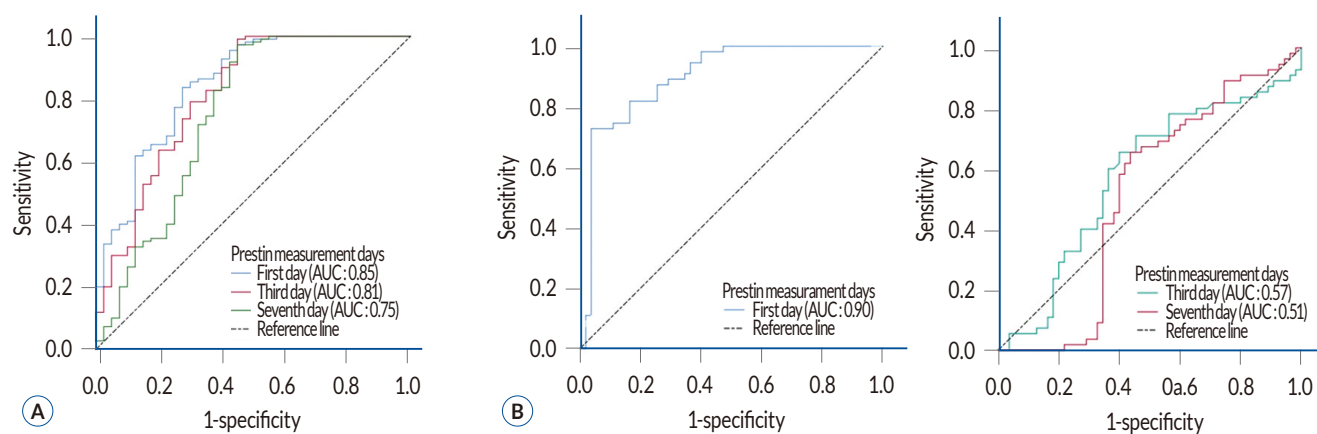


Fig. 3. A : Receiver operating characteristic (ROC) analysis plots of prestin values for trauma diagnosis. B : ROC analysis plots of prestin values for detection of severe or mild trauma (prognosis). AUC : area under the curve.

can be used in combination have also been investigated. It has been reported that patients with GCS values below 8 have a higher mortality rate, and patients with GCS values of 13 and above have a better prognosis^{10,29}. Since patients with intermediate values may vary in terms of prognosis, in this study, those with a GCS of 8 and below were determined as one group, and those with a GCS of 13 and above were determined as the second patient group.

Electrolytes such as sodium, potassium and calcium, whose levels change in patients with head trauma or multi-trauma, have been studied²². As a matter of fact, biochemical parameters such as blood glucose level, electrolyte disorders, cortisol levels, and coagulation parameters were examined to determine the severity of trauma, and their high levels were found to be associated with mortality^{10,25,26,30}. However, since these parameters were insufficient in terms of diagnosis and prognosis and may vary in many cases, more specific markers were examined²⁸. Moreover, since these parameters can be synthesized in different tissues and different diseases, their specificity may be low in patients with head trauma or multi-trauma^{1,22}. For this reason, the effect of prestin, which is released only from the intracranial region such as the cochlea and passes into the peripheral blood, on the diagnosis and prognosis of head traumas was investigated in this study, thereby providing specific and new information for the diagnosis and prognosis of head trauma.

Although many biochemical markers have been examined, the most notable studies have been conducted with myelin basic protein (MBP) and microtubule-associated protein (MAP-2)^{4,14,16}. Wiesmann et al.³¹ reported that GFAP and S100B levels were increased in the early period of trauma and this may be useful in determining prognosis together with clinical and radiological images. Some studies may suggest different results. A previous study reported that S100B levels were not reliable in predicting early prognosis of trauma, while another study was reported that it could reduce unnecessary radiological imaging. It was showed in the literature that S100B was also increased in cases such as bone fractures, widespread skin damage, fatty tissue, and muscle damage^{9,21}.

In studies conducted with NSE, Chabok et al.⁶ reported that high NSE level in the first 3 days was associated with poor prognosis. In another study, it was reported that the peak value of NSE was measured in the first 24 hours after trauma^{6,11}. A correlation has been found between MBP serum levels in se-

vere head trauma, and its increase on 4–6th days has been reported to be associated with poor prognosis. The sensitivity and specificity of MBP in terms of mortality was determined to be 87% and 100%, respectively. However, it has been reported that its use may be limited because it is not specific to the central nervous system. Papa et al.^{15,16} evaluated MAP-2 levels together with seven biochemical parameters in the cerebrospinal fluid taken in the first 24 hours of patients with severe head trauma. They reported that high MAP-2 levels can determine the six-month prognosis in terms of mortality^{15,16}. We could not find any study in the literature investigating how prestin changes in patients with head trauma, its relationship with GCS, and its diagnostic and prognostic performance in head trauma. In our study, it was determined that the prestin values on the first day were at different values in all the groups, and the prestin values on the 1st, 3rd and 7th days in the patient groups were significantly reduced compared to the control group. In addition, prestin values measured on the first day in the GCS ≥ 13 group were lower than in the GCS ≤ 8 group. On the 3rd and 7th days, although serum prestin values in the traumatized groups were lower than the control group, no significant difference was found between them.

Although some earlier studies have suggested that serum prestin levels increase following cochlear and outer hair cell damage, the majority of reports have demonstrated a decrease under these conditions. This reduction has been attributed to diminished prestin release from healthy outer hair cells as the extent of cellular damage increases. Elevated prestin levels have been reported in cases of acute acoustic trauma and drill-induced trauma during mastoidectomy³. In addition, other studies have found that serum prestin levels may decline after cochlear damage, likely reflecting reduced prestin production from a smaller number of intact outer hair cells^{18,19}. Parker et al.²⁰ explained this phenomenon with the Hidden Outer Hair Cell Damage Hypothesis, which they supported with histopathological evidence. Similarly, Chen⁷ demonstrated in a noise-exposed rat model that prolonged exposure led to profound outer hair cell loss, accompanied by decreased prestin levels. Interestingly, prestin values increased again by day 5 and returned to baseline within 4 weeks, suggesting an adaptive upregulation of prestin expression in surviving outer hair cells⁷. Consistent with these findings, our study revealed a significant reduction in prestin values during the early phase (first day) in trauma groups. A first-day prestin level below 415.77

pg/mL was identified as a threshold strongly indicative of trauma, while levels between 293.29 pg/mL and 415.77 pg/mL were associated with severe trauma. These results suggest that early serum prestin measurements may serve as a useful biomarker for detecting trauma and estimating its severity. While further studies are needed to validate these findings and to explore their potential role in clinical management, prestin appears to be a promising biomarker in the context of traumatic brain injury.

Limitations of the study

The limitations of the study include not being able to provide a correlation with a separate scoring other than GCS, not being able to evaluate it together with radiological examinations, and not being able to examine the long-term results by following the patients for a longer period of time. Another limitation is that systematic audiological assessments, such as hearing tests, were not performed for all participants. Although patients and controls with a history of acoustic trauma or prior otological surgery were excluded, the absence of objective hearing evaluations may limit the ability to fully rule out subtle auditory confounders. Future studies addressing these limitations could yield a more robust understanding of the relationship between prestin and traumatic brain injury prognosis.

CONCLUSION

We propose that first-day prestin cut-off values may serve as a valid and reliable biomarker for the diagnosis of trauma and for distinguishing between severe and mild cases. However, other factors may also influence prestin levels over time in trauma patients, and these potential confounders require detailed investigation. Furthermore, future studies should explore the combined use of prestin with other relevant biomarkers to improve diagnostic accuracy and severity assessment. To better understand prestin dynamics across different types of head injuries and its potential role in differential diagnosis, larger studies with well-defined subgroups are warranted.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was

reported.

Informed consent

Informed consent was obtained from all individual participants included in this study.

Author contributions

Conceptualization : AY, MEA, ZH; Data curation : AY, ZH, DAG, YŞÇ; Formal analysis : AY, ZH, MTH; Funding acquisition : AY; Methodology : AY, ZH, MTH; Project administration : AY, ZH; Visualization : AY, ZH, MTH; Writing - original draft : AY, ZH, MTH; Writing - review & editing : AY, ZH, MTH, YŞÇ, MEA

Data sharing

None

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