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Short Communication

Diagnostic Value of Neuron-specific Enolase in Patients with Traumatic Brain Injury Referring to Emergency Departments in 2015-2016

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ABSTRACT

Background: The aim of the present study was to determine the optimal cut-off point of neuron-specific enolase (NSE) level for diagnosis of brain damage in patients with head trauma.

Methods: This cross-sectional study was conducted on 150 patients with traumatic brain injuries (TBIs) who referred to the Emergency Department of Besat Hospital in Tehran, Iran, during 2015-2016. The neuron specific enolase (NSE) serum level was measured by obtaining peripheral blood samples from the participants at two stages, namely upon admission (i.e., the first stage) and 6 h after admission (i.e., the second stage). To determine the best NSE cut-off point, diagnostic indices, such as sensitivity and specificity, as well as positive and negative predictive values, were used by applying the performance curve. Data were analyzed using MedCalc software (version 13.3).

Results: The mean NSE serum levels of the subjects were 16.66 ± 11.32 and 17.92 ± 12.49 at the first and second stages of the study, respectively. The sensitivity and specificity of NES were respectively calculated as 1 and 0.92 at the beginning of the study. In addition, NSE showed significant direct and indirect relationships with computed tomography (CT) scan results and Glasgow Coma Scale (GCS) scores, respectively ($P < 0.001$).

Conclusion: Considering the NSE cut-off points in the present study, NSE values can be used to determine the brain damage in patients with head trauma based on gender and age group. The NSE showed a high sensitivity and specificity. In addition, an inverse correlation was observed between NSE level and GCS score.

Keywords: Accidents, Brain injuries, Traumatic, Emergency service, Hospital, Glasgow coma scale

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Introduction

Trauma is the most common cause of mortality among people under the age of 40 years (1). Traumatic brain injury (TBI) is one of the main causes of hospitalization, mortality, and physical and mental disabilities. This event accounts for 70% of the mortalities and disabilities caused by head trauma (2-4). In the United States, TBI has the incidence rate of approximately 538 per 100,000 people with a male:female ratio of 2:1 (5).

Road accidents (RAs) in Iran are more frequent than in other countries. Accordingly, these accidents account for 77% of TBIs in Iran, 48% of which involve a *motorcycle* accidents (6). The mean age of people who died in Iran due to TBI within 2009-2013 has been reported as 34-44 years (7). In general, 20% of the patients with TBI are hospitalized, and 3% of them pass away. Nonetheless, the majority of TBI cases are classified in the mild group and managed in the emergency departments. The main causes of TBI are falls, motor vehicle accidents, sport injuries, and assaults (5). This problem imposes a high financial burden on medical system annually (8). Moreover, it is accompanied by disruptive and devastating physical, cognitive, and behavioral outcomes, which can affect the function of the family and society. Regarding this, the recognition of new methods for assessing the exact impact of head injury is of great importance (9).

There are various tools for the neurological evaluation of head trauma patients and measurement of their consciousness level. Among these instruments, the Glasgow Coma Scale (GCS) is a more common and reliable tool used for the evaluation of these patients in the emergency departments (10, 11). Based on the computed tomography (CT) scan results, the pathologic findings have been found in 5-8% of patients who referred with mild TBI and appropriate consciousness (12, 13). Therefore, the outcomes are not always correlated with the findings of the initial GCS and CT scan (14).

The need for early intubation and sedation, as well as paralysis in some patients with severe head trauma, complicates the implementation of neurologic examination. Accordingly, great efforts have been made to find the biochemical markers associated with the severity of brain damage and patient prognosis. Neuron-specific enolase (NSE) is a marker, which undergoes an elevation following stroke and anoxia. This marker has a high degree of brain tissue specificity for the diagnosis of acute neuronal damage (15).

The majority of the neuronal tissues have a low level of NSE. Approximately, NSE serum level between 5-12 and 20 ng/mL in cerebrospinal fluid is considered as normal. Given the increased concentration of NSE in the cerebrospinal fluid after a head trauma and stroke, the serum NSE level can be a useful marker for the diagnosis of neuronal damage (16).

The practicality of NSE as a marker of TBI and patient prognosis has been already assessed in several studies (16-19). Various studies have emphasized the predictive role of this biomarker in TBI (16, 19-21). Olivecrona et al. showed a high level of NSE and S-100B biomarkers in patients passing away due to TBI (22). In the same vein, Böhmer et al. introduced both S100B and NSE as the predictors of brain death in severe TBI cases (21). Furthermore, de Kruijk et al. showed an increase in the NES level in patients with head trauma (23). Considering the results of previous studies, the assessment of the role of NSE in the diagnosis of head trauma is an issue of fundamental importance to find the answer to this question: Can we use NSE as a main diagnostic factor in patients with TBI?

Iran has a high rate of mortality due to head trauma (24, 25). With regard to the importance of recognizing new methods in determining the exact impact of head injury, this study aimed to determine the diagnostic value and cut-off point of NSE among the patients with TBI referring to emergency departments. For this purpose, the patients were classified based on their GCS scores, and their plasma NSE levels were measured to evaluate the correlation between GCS score and NSE level.

Materials and Methods

This cross-sectional study was conducted on 150 patients with TBI referring to the Emergency Department of Besat Hospital affiliated to the AJA University of Medical

Sciences, Tehran, Iran, from December 2015 to December 2016. The study population was selected through the convenience sampling method. The exclusion criterion was the lack of possibility to measure the NSE serum level.

The patients' demographic data were collected at the beginning of the study. To measure the NSE serum level, peripheral blood samples were obtained from all participants in two stages, namely upon admission (i.e., the first stage) and 6 h after admission (i.e., the second stage). The NES serum level was measured using an ELISA spectrophotometer (STAT FAX 2100), according to the manufacturer's instructions. The obtained samples were centrifuged, and then, kept in a refrigerator under a standard condition. Subsequently, all patients were subjected to CT scan. In addition, the patients' GCS scores were determined.

Statistical analysis

The obtained data were analyzed in Excel and MedCalc software (version 16) using some statistical tests, such as t-test and Pearson's correlation coefficient. In order to compare the efficiency of NES and GCS in the correct diagnosis of TBI, true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates were measured.

When the diagnosis was positive both in the NSE and CT scan findings, it was considered as TP. When the diagnosis was positive based on the NSE and negative according to the CT scan findings, it was regarded as FP. Moreover, the negative diagnosis based on both NSE and CT scan was considered as TN. Finally, when the diagnosis was negative according to the NSE, but positive in the CT scan, it was regarded as FN. The sensitivity, specificity, positive predictive value, and negative predictive value were also measured in the present study. The Receiver Operating Characteristic (ROC) curve was only drawn for NSE based on gender and age groups. Statistical significant level was considered at $P < 0.05$.

Ethical Approval

Regarding the research ethics, informed consent was obtained from the participants. In addition, the patients were assured about the confidentiality of the data and possibility of withdrawal from the study at any time. The study protocols were reviewed and approved by the Ethics Committee of AJA University of Medical Sciences, Tehran (Ethical code: IR.AJAUMS.1395.39).

Results

According to the results of the study, the mean age of the participants was 36.78 ± 18.44 years (age range: 3-89 years). About 82.7% of the patients in this study were male. The mean GCS scores were 12.19 ± 3.34 (range: 4-15) and 11.9 ± 4.02 (range: 3-15) at the first and second stages of the study, respectively. Moreover, the mean NSE levels were 16.66 ± 11.32 (range: 2.9-53.9) and 17.92 ± 12.49 (range: 3.1-59.7) at the first and second research stages, respectively. The distribution of other descriptive data is presented in Table 1.

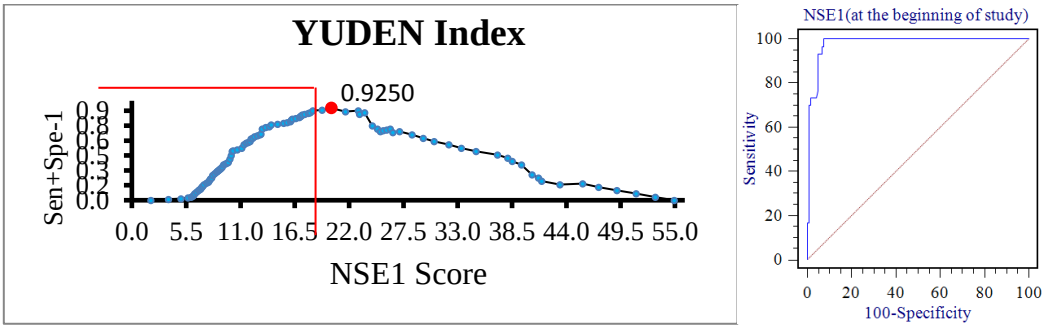
Table 1. Distribution of demographic and clinical information

Variables		Percentage (%)	Variables		Percentage (%)
Age	≥25	31.3	Computed tomography scan	With sign	45.6
	26-45	39.3		Without sign	54.7
	<45	29.3			
GCS upon admission	Mild	52.7	GCS 6 h after admission	Mild	54.7
	Moderate	27.3		Moderate	21.3
	Severe	20		Severe	24

GCS: Glasgow coma scale.

Upon admission (i.e., the first stage of the study), NSE test was positive in 20% of the patients, who were diagnosed with severe brain damage based on the GCS. However, this test was negative in 80% of the patients whose GCS scores were indicative of moderate or mild brain damage. In order to detect the optimal NSE cut-off point, the ROC curve was drawn (Figure 1).

The area under the curve (AUC) was expected to be higher than 0.5. The AUC was estimated to be 0.98%, which is accepted with 95% confidence (Z = 50.6, P < 0.001). Based on the ROC curve, the Youden's index (J) was calculated as 0.92 with a cut-off point of 20.25, as shown in Figure 1. Table 2 demonstrates the distribution and ROC curve data of NSE at the first stage of the study based on gender and various age groups.



(A) **(B)**

Figure 1. Optimal neuron-specific enolase cut-off point upon admission (A) and Youden's index (B).

Table 2. Distribution and receiver operating characteristics curve data of neuron-specific enolase upon admission based on gender and age group

		NSE Outcome		AUC					Youden's Index			
	Variables		Percentage (%)	AUC	SD	CI	Z	P-value	Value	SD	CI	Cut-off
Gender	Female	Positive	11.54	1.00	--	0.86-1.0	---	<0.001	1.00	--	--	20.25
		Negative	88.46									
	Male	Positive	21.77	0.97	0.01	0.93-0.99	43.88	<0.001	0.91	0.002	0.83-0.95	22.9
		Negative	78.23									
Age (years)	≤25	Positive	17	0.96	0.02	0.86-0.99	18.42	<0.001	0.92	0.01	0.76-0.97	19.25
		Negative	83									
	25-45	Positive	20.3	0.98	0.01	0.91-1.0	41.67	<0.001	0.91	0.003	0.808-0.95	21.55
		Negative	79.8									
	≥25	Positive	22.7	0.98	0.01	0.89-1.0	40.33	<0.001	0.94	21	0.77-1.0	21.25
		Negative	77.3									

NSE: Neuron-specific enolase, AUC: Area under curve, SD: Standard deviation, CI: Confidence interval. P-value less than 0.05 is statistically significant.

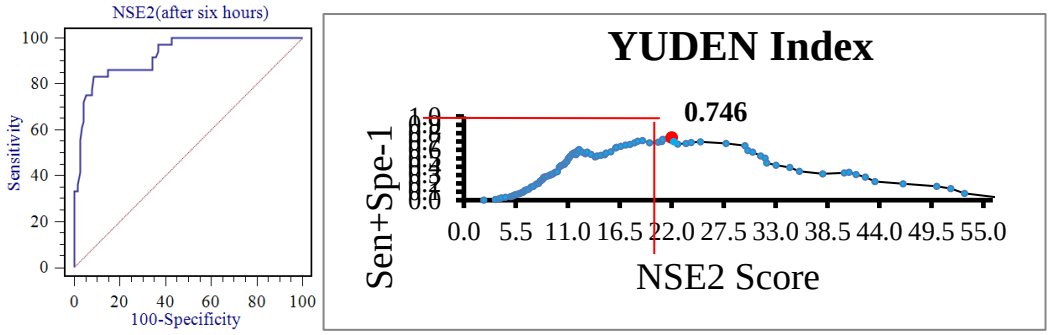
Upon admission, the sensitivity and specificity of NES were estimated as 1 (95%CI: 0-88) and 0.92 (95%CI: 0.86-0.96), respectively, based on the Youden's index of 0.92. The positive and negative predictive values were 73.2 (95%CI: 55.5-86.7) and 100 (95%CI: 96.8-100), respectively. Moreover, the positive and negative likelihood ratios were calculated as 13.33 (95%CI: 7.1-25) and 0, respectively. Table 3 displays the sensitivity, specificity, positive and negative predictive values, as well as positive and negative likelihood ratio of NES based on gender and various age groups.

Table 3. Sensitivity, specificity, and positive and negative likelihood ratios upon admission based on gender and age group

Variables		Index	Value	CI
Gender	Female	Sensitivity	1.00	0.292-1.0
		Specificity	1.00	0-852-1.0
		Positive likelihood ratio	--	---
		Negative likelihood ratio	0	---
	Male	Sensitivity	1.00	0.87-1.00
		Specificity	0.918	0.844-0.964
		Positive likelihood ratio	12.12	6.2-23.5
		Negative likelihood ratio	0	---
Age (years)	≤25	Sensitivity	1.00	0.63-1.0
		Specificity	0.92	0.79-0.98
		Positive likelihood ratio	13.0	4.4-38.6
		Negative likelihood ratio	0	---
	25-45	Sensitivity	1.0	0.73-1.0
		Specificity	0.91	0.79-0.97
		Positive likelihood ratio	11.75	4.6-30
		Negative likelihood ratio	0	---
	≥25	Sensitivity	1.0	0.69-1.0
		Specificity	0.91	0.803-0.99
		Positive likelihood ratio	17.0	4.4-65.2
		Negative likelihood ratio	0	---

CI: Confidence interval.

Six hours after admission, the NSE test was positive in 24% of the patients, who were diagnosed with severe brain damage based on the GCS. Nonetheless, it was negative in 76% of the patients whose GCS scores indicated a moderate or mild brain damage. Moreover, the AUC was equal to 0.92%, which is accepted with 95% confidence (Z = 17.18, P < 0.001; 95%CI: 0.87-0.96). Based on the ROC curve, the Youden's index was calculated as 0.74 with a cut-off point of 22.05 (Figure 2). Table 4 demonstrates the distribution and ROC curve data of NSE in terms of gender and various age groups 6 h after admission.



(A) **(B)**

Figure 2. Optimal neuron-specific enolase cut-off point six hours after admission (A) and Youden's index (B).

Table 4. Distribution and receiver operating characteristics curve data of neuron-specific enolase six hours after admission based on gender and age group

		NSE Outcome		AUC					Youden's Index			
	Variables		Percentage (%)	AUC	SD	CI	Z	P-value	Value	SD	CI	Cut-off
Gender	Female	Positive	19.2	0.98	0.02	0.83-1	20.36	<0.001	0.95	0.001	0.76-1	18.6
		Negative	80.8									
	Male	Positive	25	0.91	0.02	0.85-0.95	14.85	<0.001	0.74	0.01	0.58-0.86	22.05
		Negative	75									
Age (years)	≤25	Positive	19.1	0.904	0.05	0.78-0.97	7.47	<0.001	0.72	0.01	0.5-0.89	22.15
		Negative	80.9									
	25-45	Positive	20.3	0.93	0.03	0.84-0.98	11.67	<0.001	0.83	0.01	0.59-0.95	23.5
		Negative	79.7									
	≥25	Positive	34.1	0.92	0.04	0.79-0.98	10.19	<0.001	0.66	0.01	0.46-0.76	27.55
		Negative	65.9									

NSE: Neuron-specific enolase, AUC: Area under curve, SD: Standard deviation, CI: Confidence interval. P-value less than 0.05 is statistically significant

At the second stage of the study, the sensitivity and specificity of NES were evaluated as 0.83 (95%CI: 0.67-0.93) and 0.91 (95%CI: 0.84-0.95) based on the Youden's index, which was equal to 0.74. Furthermore, the positive and negative predictive values were 66.1 (95%CI: 47.3-81.7) and 96.4 (95%CI: 91.2-99), respectively. Moreover, the positive and negative likelihood ratios were 9.5 (95%CI: 5.2-17.5) and 0.18 (95%CI: 0.09-0.4), respectively. Table 5 presents the sensitivity, specificity, as well as positive and negative predictive values of NES 6 h after admission based on gender and various age groups.

Table 5. Sensitivity, specificity, and positive and negative likelihood ratios six hours after admission based on gender and age groups

Variables		Index	Value	CI
Gender	Female	Sensitivity	1	0.47-1
		Specificity	0.95	0.76-0.99
		Positive likelihood ratio	21	3.1-142.2
		Negative likelihood ratio	0	--
	Male	Sensitivity	0.83	0.66-0.94
		Specificity	0.903	0.82-0.95
		Positive likelihood ratio	8.67	4.6-16.4
		Negative likelihood ratio	0.18	0.08-0.4
Age (years)	≤25	Sensitivity	0.77	0.4-0.97
		Specificity	0.94	0.82-0.99
		Positive likelihood ratio	14.78	3.7-59.5
		Negative likelihood ratio	0.23	0.07-0.8
	25-45	Sensitivity	0.91	0.61-0.99
		Specificity	0.91	0.79-0.97
		Positive likelihood ratio	10.77	4.2-27.9
		Negative likelihood ratio	0.09	0.01-0.6
	≥25	Sensitivity	0.66	0.38-0.88
		Specificity	1	0.88-1
		Positive likelihood ratio	--	--
		Negative likelihood ratio	0.33	--

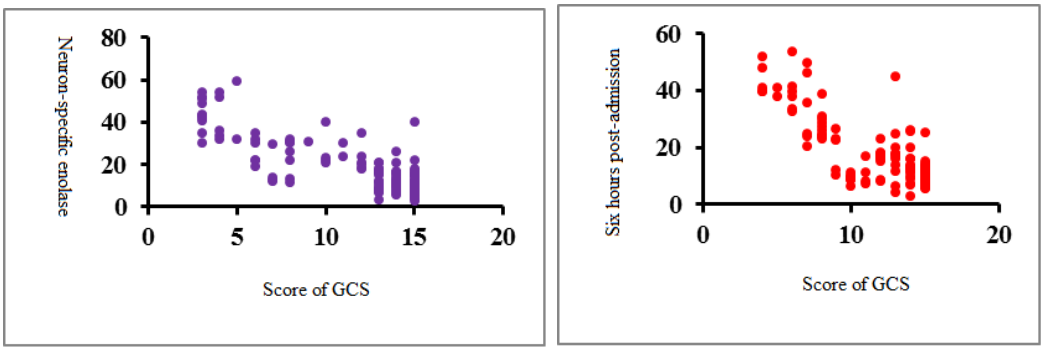
CI: Confidence interval.

The comparative evaluation of the NSE and CT scan results is shown in Table 6. As indicated in this table, there was a significant difference between the results of the NSE and CT scan both upon admission ($t = 6.81$, $P < 0.005$) and 6 h after admission ($t = 6.24$, $P < 0.005$). Figure 3 illustrates the relationship between the NSE and GCS upon admission and 6 h after admission. The comparison of the NSE and GCS results revealed a significant correlation between these tests both at the first ($r = -0.66$, $P \leq 0.005$) and second stages ($r = -0.73$, $P \leq 0.005$) of the study.

Table 6. Comparison of neuron-specific enolase and computed tomography scan results

Time	Outcome	Number	Mean	SD	t	P-value
Upon admission	Positive	68	22.71	13.17	6.81	≤0.005
	Negative	82	11.64	6		
6 h after admission	Positive	68	24.16	14.02	6.24	≤0.005
	Negative	82	12.74	8.04		

SD: Standard deviation.



(A) **(B)**

Figure 3. Relationship between neuron-specific enolase and Glasgow coma scale upon admission (A) and six hours after admission (B).

Discussion

The present study was conducted to determine the diagnostic value of NSE in patients with trauma. The NSE showed high sensitivity and specificity with the cut-off point of 20.25, which is consistent with the results of other studies (18, 20, 21, 26, 27). At the first stage of the study (i.e., upon admission), the NSE sensitivity was equal in two genders, while its specificity was higher in females compared to males. Nevertheless, at the second stage of the study (i.e., 6 h after admission), both sensitivity and specificity were higher in females than those in males.

Based on the evidence, S100 b, NSE, and glial fibrillary acidic protein have a moderate specificity for the diagnosis of neurological injuries. These biomarkers are detectable in the serum of patients and demonstrate the systemic manifestations of these insults. Serum and cerebrospinal fluid levels of these biomarkers contribute to the prediction of severe TBI outcome (20). There are multiple studies examining the relationship of the levels of these biomarkers with intracranial neuronal cellular injury (28, 29). However, there are limited data on the relationship of these biomarkers with post-traumatic cerebral hypoxia and ischemia.

Low sensitivity of these biomarkers for CH is indicative of their failure to predict the probability of cerebral hypoxia incidence. On the other hand, the high specificity of these biomarkers for moderate and sever cerebral hypoxia reveal that low levels of them are highly associated with a time period without the development of cerebral hypoxia (20).

Approximately, 73.2% of the patients with brain damage were correctly diagnosed. The negative likelihood ratio was obtained as 0, indicating no possibility of diagnosing patients with brain injury as healthy people. Likewise, the calculation of the positive likelihood ratio showed that NES could diagnose the patients with brain damage with a high probability. Accordingly, this test had a very low probability of positive diagnosis in healthy people.

There are several studies investigating the practicality of NSE as a marker of TBI and patient prognosis (16, 18, 19, 26, 30-32). The predictive power of these biomarkers in the traumatic brain injury has been emphasized in various studies (16, 19-21). Based on a study performed by Olivecrona et al., patients with the GCS score of 3 and those died had a higher level of NSE and S-100B biomarkers in comparison to those with the GCS score of 4-6 (22). Similarly, Böhmer et al. introduced both S100B and NSE as the predictors of brain death in severe TBI. Furthermore, they showed that NSE had a higher predictive power than S100B in this regard (21).

In another study by de Kruijk et al., an insignificant increase was observed in the NES level of patients with head trauma, while the level of S-100B protein was significantly

elevated (23). These differences can be due to the difference in various factors, such as sample conditions and type of applied instrument. In general, the evidence confirms the role of NSE in the diagnosis of head trauma; accordingly, it is used as a main diagnostic factor in patients with brain damage (16, 19-21).

Meric et al. (2010) investigated the correlation between NSE and GCS results regarding the severity of brain injury among 80 traumatic patients. They showed that the level of NSE was normal among the patients with general trauma and no head injury. However, they reported a small elevation (but not significant) in the NSE level among the patients with mild head trauma. Furthermore, they found an increase in the level of NSE among the patients with moderate and severe head trauma. In their study, the sensitivity and specificity of NSE were calculated as 87% and 82.1%, respectively, with the cutoff point of 20.52 and AUC of 0.931 (26), which are largely consistent with the findings of the present study.

Consistent with the findings of other studies (26, 33), the present study revealed an inverse correlation between NSE value and GCS score. In a study conducted by Sogut et al. GCS showed a significant relationship with NSE level. In the mentioned study, the GCS score of ≤ 8, age, and NSE levels were proposed as the main predictors of mortality in patients with head trauma. Moreover, they showed that NSE can be used as an alternative indicator to the GCS for the management of head injury during the early post-traumatic period (34). In a similar study, a strong relationship was detected between NSE and GCS score (35).

In a study performed by Meric et al., the GCS scores were inversely correlated with NSE level in the patients with severe, moderate, and mild head trauma; however, this relationship was not observed in other groups (26). On the other hand, Olivecrona et al. reported a weak correlation between NSE level and GCS score (22). Moreover, in a study conducted by Ross et al. no correlation was observed between serum NSE levels and GCS values in patients with severe head trauma. Nonetheless, they found a correlation between these two parameters one month after trauma (36). Similarly, Raabe et al. detected no correlation between the serum NSE levels and GCS values 6 months after admission in patients with severe head trauma (37).

These discrepancies can be due to several reasons. The studies of Ross et al. (1996) and Raabe et al. were conducted with a nearly 20-year interval from the present study and is different in design (36, 37). In addition, Raabe et al. only investigated patients with severe head trauma and measured NSE levels every 24 h for 10 days (37).

Furthermore, in a study conducted by Zaheer et al. a strong inverse correlation was observed between GCS and NSE in patients with acute ischemic stroke (38). These findings are consistent with those obtained by Brea et al. who indicated a correlation between the peak concentration of NSE and stroke severity (39). According to the findings of the present study, NSE level was higher in patients with positive CT scan findings upon admission and 6 h later compared to those with negative CT scan findings, which is consistent with the results of other similar studies (20-22, 27, 31, 35, 40).

Currently, there is no way to predict the secondary brain injury in patients with TBI. The patients with head trauma are often the victims of polytrauma. They need to receive the interventions targeted toward the management of other injuries, such as extremity fractures. Furthermore, they should be provided with non-neurological critical care. If cerebral edema or hypoxia develop in patients with Traumatic *brain injury*, the decision on the appropriateness of interventions is very hard. Systemic reflections of these cerebral insults could help clinicians decide about the appropriate timing of interventions.

The results of the present revealed the efficiency of NSE as a proper marker for brain injury. However, NSE can be found in erythrocytes, in addition to the neuronal tissue. Therefore, it may be misleading in patients with hemolysis. Moreover, NSE has a long biological half-life (i.e., less than 20 h) and may be affected by sample timing.

One of the main strength of the present study is the control of some variables affecting neurologic outcome, such as age and gender. Moreover, the effect of time on the serum NSE levels was controlled by measuring this marker upon the patient's admission and 6 h after trauma.

Future studies are recommended to assess whether NSE level is a proper marker for the determination of neurologic prognosis in patients with different degrees of trauma. Further

studies are also suggested to compare NSE with other similar markers, such as S100B, and assess brain damage 12, 24, and 48 h after trauma. In addition, it is recommended to investigate a larger sample size and people with an age less than 18 years.

Although the diagnostic efficacy of NSE in patients with TBI has been previously assessed in Iran, the reconsideration of this issue is very important with regard to the higher frequency of road accidents in Iran compared to other countries. This study was the first attempt investigating NSE in rheumatoid arthritis patients. However, the serum NSE levels was not evaluated in longer intervals from trauma.The small sample size was the main limitation of this study. Therefore, the results of this study cannot be generalized to other populations. Accordingly, it is recommended to perform larger studies with larger sample size to obtain more accurate results.

Conclusion

According to the findings of the present study, NSE showed a high sensitivity and specificity. Therefore, this enzyme can be used for the diagnosis of the patients with head trauma. In the present study, the majority of the patients with brain damage were diagnosed correctly. Furthermore, there was no possibility of diagnosing the patients with brain injury as healthy people. The results also demonstrated an inverse correlation between NSE level and GCS score.

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Conflict of interests

The authors have no conflict of interests.

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