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THE CORRELATION BETWEEN NEURON-SPECIFIC ENOLASE (NSE) SERUM LEVEL AND TRAUMATIC BRAIN INJURY SEVERITY

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Abstract
Traumatic brain injuries (TBIs) are a health and socio-economic problem worldwide, both in low- and high-income countries, that affects all age groups. Computed Tomography (CT) is a diagnostic modality that can be used to assess brain damage. However, there are some limitations in the use of CT in TBIs. Therefore, biomarkers are expected to be a solution to identify brain injuries. Neuron-Specific Enolase (NSE) is a more practical and cheaper alternative. It does not require patient mobilization, especially for patients with severe TBIs, to accompany clinical examinations and CT. Methods: A cross-sectional design was used to determine the correlation between Neuron Specific Enolase (NSE) serum levels and the severity of TBIs at RSUP Dr. M. Djamil, Padang. Results: The study found that most patients were 23 men (76.7%), consisting of adults (40.0%). The majority of patients had mild traumatic brain injury (GCS 13-15) in 18 people (60.0%). The cut-off point for serum NSE was 6.6 ng/ml using the ROC curve. There was a negative correlation between serum NSE levels and the severity of TBI (r=-0.211). Conclusion: The correlation of serum NSE levels with the severity of TBI was very weak.
Keywords: *Traumatic brain injury, Neuron-Specific Enolase, NSE, Glasgow Coma Scale*

INTRODUCTION

Traumatic brain injury (TBI) is defined as an impairment of brain function caused by external forces, including falls, blows, or explosions. Traumatic brain injury is one of the most challenging health issues and a leading cause of trauma-related morbidity and mortality.[1–5]

Traumatic brain injury constitutes a major global health and socioeconomic burden, affecting people of all ages in both low- and high-income countries. According to the World Health Organization (WHO), more than 1.2 million people die annually from road accidents, and 20–50 million sustain non-fatal injuries. Around 90% of these deaths occur in low- and middle-income countries.[6] Traumatic brain injury ranks as the third leading cause of death after heart disease and stroke. In the United States, approximately 1.7 million people experience TBIs annually, with 275,000 hospitalized and 52,000 dying from their injuries. Around 1.3 million

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are treated and discharged from emergency departments, and approximately 90,000 suffer long-term disability. Although the death rate from traumatic brain injury remains low (6 per 100,000), the societal cost remains high. In Europe, the incidence of traumatic brain injury is recorded per 100,000 population annually, and the total mortality from fatal TBIs in specific populations is also recorded per 100,000 population per year. (Schouten and Maas, 2011; Roozenbeek, Maas and Menon, 2013; Neher et al., 2014; Faried et al., 2017; Manivannan et al., 2018a; Dewan et al., 2019; Brazinova et al., 2021; Mozaffari et al., 2021).

The 2018 Basic Health Research (RISKESDAS) survey in Indonesia reported a traumatic brain injury prevalence of 11.9%. Most cases involved males (11.9%), mainly due to occupational and activity-related factors, such as drivers and students who frequently travel and often disregard traffic regulations. According to the Central Bureau of Statistics (BPS) of West Sumatra in 2021, there were 2,973 traffic accidents. Padang City recorded the highest number of accidents in West Sumatra with 705 incidents, while the Mentawai Regency had the fewest with only 15 cases. TBIs can occur across all age groups, but the highest incidence is among individuals aged 15–25 years. TBI is recognized as a leading cause of death and disability among young adults [15–18]

TBIs are divided into primary and secondary injuries. Primary traumatic brain injury refers to the immediate damage resulting from mechanical trauma to the skull and brain tissue. Secondary injury occurs as a progression from the primary injury and includes complications known as post-primary injury. Causes of secondary injury may be intracranial (e.g., epidural hematoma, subdural hematoma, intracerebral hematoma, cerebral edema, increased intracranial pressure [ICP]) or extracranial/systemic (e.g., hypertension, hypotension, hypercapnia, hypoxemia, anemia, hypoglycemia, hyperthermia, and sepsis. [16,19–21]

Computed Tomography (CT) is a diagnostic modality to assess brain damage in cerebral vasculature and neural tissue. However, CT imaging for traumatic brain injury faces several limitations, including restricted availability of equipment and trained operators, lengthy examination time, and relatively high costs. As such, biomarkers are anticipated to serve as a solution to identify brain injuries. Unlike in other diseases where biomarkers help determine diagnosis and treatment, brain injury biomarkers are used to assess severity, detect anatomical and cellular abnormalities, and evaluate the extent of injury.[19,22,23]

Neuron-Specific Enolase (NSE) is a practical and affordable alternative biomarker that does not require patient mobilization—an essential advantage for patients with severe TBI who require complete bed rest. NSE is a glycolytic enzyme with a molecular weight of 78 kDa, found primarily in neuronal and neuroendocrine cells, and rare tumors such as small cell lung carcinoma, melanoma, and neuroblastoma. NSE is also present in platelets and erythrocytes and is released passively following cellular damage rather than actively secreted into the serum. Compared to other brain injury biomarkers, NSE is highly sensitive, stable, and shows a rapid increase after trauma.[19,24] In addition to NSE, other biomarkers with significant sensitivity or specificity for TBI include S100 calcium-binding protein B (S100B), Glial Fibrillary Acidic Protein (GFAP), Myelin Basic Protein (MBP), Ubiquitin C-terminal Hydrolase L1 (UCHL1), tau protein, and Alpha-II spectrin. [16,25–27]

NSE has been found to increase in both cerebrospinal fluid (CSF) and

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peripheral serum, with greater elevations associated with higher mortality and more severe GCS scores in both adults and children. However, since NSE is also naturally expressed in erythrocytes, its levels can be elevated due to hemolysis or contamination of CSF with peripheral blood. [28–31]

A study on patients with severe diffuse axonal injury showed that serum NSE levels had 100% sensitivity and specificity in predicting post-injury mortality at 950 ng/mL concentrations.[32] Elevated NSE levels have also been observed in patients with secondary hypoxic traumatic brain injury. Initial and peak NSE levels were higher in non-survivors than in survivors. One study showed that, compared to S100B, NSE levels were more closely related to the prediction of brain death following severe traumatic brain injury.[16,33]

Based on the background above, the authors aim to determine whether there is a correlation between serum Neuron-Specific Enolase (NSE) levels and Glasgow Coma Scale (GCS) scores, which indicate the severity of traumatic brain injury.

MATERIALS AND METHODS

This study falls within the fields of neurology and clinical pathology. The research was conducted at the Emergency Department of Dr. M. Djamil Central General Hospital in Padang, where patient sampling occurred. Laboratory analysis was performed at the Biomedical Laboratory of the Faculty of Medicine, Andalas University, and the research period extended from March to October 2022.

This analytic observational study with a cross-sectional design aimed to evaluate the correlation between serum Neuron-Specific Enolase (NSE) levels and the severity of traumatic brain injury in patients at Dr. M. Djamil Hospital, Padang.

All patients with TBIs presenting to the Emergency Department of Dr. M. Djamil Hospital within 48 hours of trauma in December 2022 were included according to the inclusion and exclusion criteria. The study sample comprised 30 traumatic brain injury patients.

Univariate analysis involved descriptive statistics presented in frequency distribution tables and narrative form. Bivariate analysis was performed to assess the correlation between the independent and dependent variables using the Spearman rho correlation test.

RESULT AND DISCUSSION

Based on 30 samples of traumatic brain injury patients at Dr. M. Djamil Central General Hospital, Padang, the results are as follows:

Table 1. Frequency Distribution of Head Injury by Sex

Sex	Frequency (f)	Percentage (%)
Male	23	76.
Female	7	23.3
Total	30	100

Most patients were male (23 people, 76.7%), followed by female (7 people, 23.3%).

Table 2. Frequency Distribution of Head Injury by Age

Age Group	Frequency (f)	Percentage (%)
Adolescents (18–25)	11	36.7

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Age Group	Frequency (f)	Percentage (%)
Adults (26–45)	12	40.0
Elderly (>45)	7	23.3
Total	30	100

The most affected age group was adults (26–45 years), with 12 patients (40.0%), followed by adolescents (11 patients, 36.7%) and the elderly (7 patients, 23.3%).

Table 3. Frequency Distribution of Head Injury by Severity (Based on GCS)

Severity Level	Frequency (f)	Percentage (%)
Mild (GCS 13–15)	18	60.0%
Moderate (GCS 9–12)	6	20.0%
Severe (GCS 3–8)	6	20.0%
Total	30	100%

The most frequent severity was mild traumatic brain injury (18 patients, 60.0%).

Table 4. ROC Curve Coordinates for Serum NSE Levels

NSE Level (ng/ml)	Sensitivity	Specificity
6.1	0.722	0.250
6.2	0.667	0.250
6.2	0.667	0.333
6.3	0.667	0.417
6.4	0.611	0.500
6.6	0.611	0.583
6.6	0.611	0.667
6.6	0.556	0.667
6.7	0.500	0.750
6.8	0.444	0.750

The ROC curve analysis determined the serum NSE cut-off point to be 6.6 ng/ml.

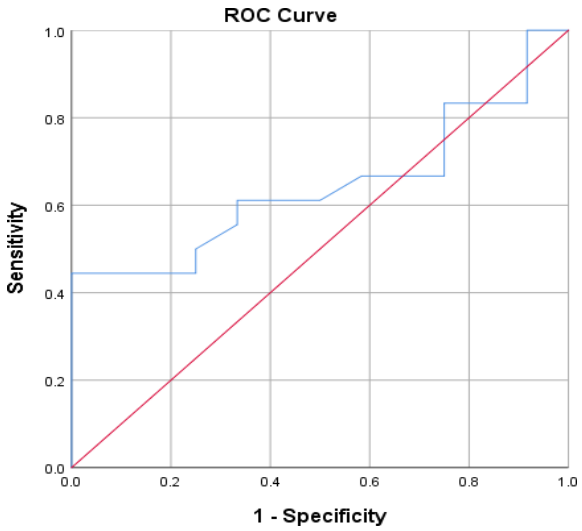

Figure 1. ROC curve

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Table 5. Correlation Between Serum NSE Levels and TBI Severity

NSE Category	Mild	Moderate	Severe	Total	Correlation (r)	p-value
Normal (≤6.6 ng/ml)	7 (38.9%)	3 (50.0%)	4 (66.7%)	14	-0.211	0.262
Elevated (>6.6 ng/ml)	11 (61.1%)	3 (50.0%)	2 (33.3%)	16		
Total	18	6	6	30		

From the sample of 30 samples, 16 patients had elevated serum NSE levels, while 14 had normal levels. The correlation between NSE levels and traumatic brain injury severity was not statistically significant (p = 0.262), and the correlation was negative and very weak (r = -0.211).

Frequency of Traumatic Brain Injury by Sex

Based on the interview (anamnesis) of 30 traumatic brain injury patients at Dr. M. Djamil Hospital Padang, the most common sex was male (23 patients or 76.7%). This aligns with a study by Hanura Aprilia (2016), which found that among 80 traumatic brain injury cases, males accounted for 65% (52 cases).[34] Similarly, research by Gusti et al. showed that males made up 79.2% (42 of 53 cases). These findings suggest that males are more likely to sustain TBIs, mainly due to traffic accidents. Previous studies have shown that male motorcyclists are twice as likely as females to be involved in traffic accidents. Overall, 80.8% of traffic accident victims are male. Traffic accidents are the leading cause of trauma compared to other causes.[35]

A study by Dian Ayu Hamama Pitra (2021) also found that males dominated traumatic brain injury cases (43 patients, 71.1%), compared to females (17 patients, 28.3%). This disparity is attributed to higher traffic involvement among males and the fact that traffic accidents are the leading cause of TBIs (96.7%).[36]

Sex differences in health issues can also be linked to males' greater activity levels, which increase their exposure to risk factors. Occupational roles are another contributing factor—men are more likely to work in high-risk jobs such as construction and electronics service.[37]

Munivenkatappa et al. found that females had a higher proportion of TBIs among children (<18 years). Mild TBIs were more common in female children and elderly groups, with falls being a more frequent mechanism than road traffic accidents. Interestingly, only older women showed more abnormal findings on CT brain scans.[38,39]

Frequency of Traumatic Brain Injury by Age

From the sample of 30 traumatic brain injury patients, the majority were in the adult group (26–45 years), with 12 cases (40.0%). This matches findings by Astrid C.A. et al., who reported that this age group—characterized by high mobility and limited awareness of protective gear—has an increased risk. Additionally, this group is susceptible to focal brain lesions due to brain atrophy and tearing of bridging veins.[40] Adults also tend to have less experience and knowledge about road systems, making them less capable of anticipating or reacting to hazards.[34]

In contrast, a study by Noviyanter et al. found that the adolescent group (15–24 years) had the highest number of cases (37 patients, 33.33%). Risk factors in this group include reckless driving, high-speed vehicle use, low awareness, intoxication,

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and involvement in fights or work-related accidents. Adolescents are also considered emotionally and mentally immature, making them more prone to risky situations that could lead to TBIs.[41]

Frequency of Traumatic Brain Injury by Severity

Based on Glasgow Coma Scale (GCS) scores, mild traumatic brain injury was the most common severity, found in 18 of 30 patients (60.0%). This is consistent with Danang B.U. et al., who reported that 46.7% (28 of 60 cases) were mild. [42]Similarly, Mede Favian B.G. et al. (2022) found that 48 of 86 cases (55.8%) involved mild TBI.[43]

Mild traumatic brain injury is the most frequent type of head trauma. This is often related to the injury mechanism and indicates that many cases were not severe, and patients retained full consciousness at the time of trauma.[43]

Dewan et al. reported that mild TBI accounted for 81.02% of cases globally, moderate TBI 11.04%, and severe TBI 7.95%. Approximately 69 million people suffer TBIs annually, with mild TBI affecting 55.9 million and severe TBI affecting 5.48 million individuals per year.[44]

In contrast, Usi Sukorini et al. found that severe TBI was most common (24 of 51 cases, 47.1%), followed by mild (43.1%) and moderate (9.8%).[45] Yuliarni Syafrita reported moderate TBI as the most frequent (36.1%), with mild and severe each accounting for 23 cases.[46]

Cut-off Point of Serum NSE Levels

The ROC curve analysis of 30 samples analyzed using the Enzyme-Linked Immunosorbent Assay (ELISA) method revealed that the serum NSE cut-off point was 6.6 ng/ml. In comparison, Usi Sukorini et al. reported a cut-off value of 21.7 ng/ml based on Electrochemiluminescence Immunoassay (ECLIA) in 51 TBI patients. They also categorized onset time into <12 and 12–24 hours.[45]

Feng Cheng et al. used a previous study to set a 20 mg/L cut-off. To achieve 100% sensitivity for mortality prediction (i.e., no false negatives), thresholds ranged from 11.62 to 20 mg/L with a specificity of 0.33–0.45. For poor outcomes, a 20 mg/L threshold yielded 60% specificity.[47]

Correlation Between Serum NSE Levels and TBI Severity

In this study, ELISA analysis found the following:

1. Among 18 mild TBI patients, 11 had elevated NSE (>6.6 ng/ml), and 7 had normal levels.
2. Among six moderate TBI patients, three had elevated and three had normal levels.
3. Among six severe TBI patients, four had elevated and 2 had normal levels.

In contrast, Usi Sukorini et al. found that among 22 mild TBI patients, 21 had normal NSE, and one had elevated NSE. Among 5 moderate cases, three were normal, and two were elevated. Among 24 severe cases, 13 were elevated, and 11 were normal.[45]

Spearman correlation analysis showed no significant relationship ($p = 0.262$), with a weak negative correlation ($r = -0.211$). This aligns with Thelin et al. (2016), who reported that NSE had weak short-term associations but good long-term predictive value for mortality and survival.[48]

Limitations of NSE as Biomarker

NSE has low diagnostic value in TBI. One major limitation is that NSE is also expressed in red blood cells, making it susceptible to hemolysis-related bias.

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Hemolysis correction is recommended when measuring NSE.[49]

NSE also has low sensitivity during the early post-trauma phase. A 2015 study by Olivecrona et al. comparing NSE and S100B with GCS scores found that S100B had stronger correlations—particularly in severe cases—while NSE showed no clear relationship with either mild or severe TBI. However, NSE showed strong sensitivity during the first 72 hours post-trauma in predicting mortality. [50]

A 2020 study by Caroline Lindblad et al. supported this, showing that NSE had a delayed correlation with cerebrospinal fluid (CSF) compared to S100B. NSE has an effective half-life of 48–72 hours in serum, while S100B peaks earlier at 24 hours. This delay in serum detection makes S100B a more immediate biomarker, while NSE may be more suited for delayed assessments.[51]

In contrast, Yuliarni Syafrita and Nora Fitri found a significant association between NSE levels and TBI severity. Their study, with a large sample size (72 cases), used numerical analysis and post hoc tests to show significant differences in NSE between mild vs. severe and moderate vs. severe TBI, though not between mild and moderate groups. The study's advantage was proportional distribution across severity levels and serial measurements of NSE.[46]

Prognostic Value of NSE

Although NSE has weak diagnostic power, it has substantial prognostic value. Feng Cheng et al. (2014) found that high NSE levels significantly correlated with mortality and neurological outcomes in TBI patients. Serum NSE levels between 11.62 and 20 mg/L showed 100% sensitivity in predicting mortality and poor outcomes. In 8 studies assessing the Glasgow Outcome Scale (GOS), poor-outcome patients consistently had significantly higher NSE levels than those with good outcomes.[47]

CONCLUSION

The most common sex among head injury patients at Dr. M. Djamil General Hospital, Padang, was male, accounting for 23 of 30 patients. The most common age group was adults aged 26–45, with 12 patients. Based on Glasgow Coma Scale (GCS) scores, the most frequent severity was mild head injury (GCS 13–15), found in 18 patients. The cut-off point for serum NSE levels was determined to be 6.6 ng/ml using the ROC curve. There was no significant relationship between serum NSE levels and the severity of head injury ($p > 0.05$). The correlation was negative and weak, indicating an inverse but non-meaningful association.

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