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NEURON SPECIFIC ENOLASE LEVELS' RELATIONSHIP WITH CT SCAN IMAGES ON HEAD INJURY PATIENTS

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ABSTRACT

Head injuries can cause closed injuries, or open injuries that can penetrate the skin, starting from the skin as the outermost layer, to the bones of the skull, blood vessels of the brain, and brain tissue as cranio-cerebral injuries. The authors wanted to prove whether there is a picture between NSE serum levels and a CT scan of the head that describes the severity of a head injury. The type of research used in this research is analytic observational research. The study design in this study was a cross sectional which aims to describe the levels of Neuron Specific Enolase (NSE) serum with CT scan images of head injured patients at RSUP Dr. M. Djamil City of Padang. This research was conducted in the Emergency Room of RSUP Dr. M. Djamil, Padang City as the sampling location and the Biomedical Laboratory of the Faculty of Medicine, Andalas University as the research location and the research time starts from February to June 2023. Head injury patients who underwent head CT scans at the M.Djamil Hospital Padang Emergency Room were found with the following characteristics: age 20-29 years, male sex, CT scan of the head in the form of MLS<5mm/cistern narrowing, increased NSE level, severity mild head injury (GCS 13-15).

INTRODUCTION

Head injury or Traumatic Brain Injury (TBI) according to the Brain Injury Association of America, is a damage to the head, not congenital or degenerative in nature, but caused by an attack or physical impact from outside, which can reduce or change consciousness which causes damage to cognitive abilities, and physical function (Blazer et al., 2019).

Head injuries are divided into primary head injuries and secondary head injuries. Primary head injury is an injury caused by mechanical trauma to the head bones and brain tissue. Meanwhile, secondary head injury is an advanced stage of primary brain damage or is called a post-primary injury. The overall long-term neurological and pathological outcome after TBI is due to a combination of primary damage (physical contact; occurs at the time of impact) and secondary damage (due to activation of pathological mechanisms; begins within minutes and continues for months) (Pavlovic et al., 2019).

Head injuries can cause closed injuries, or open injuries that can penetrate the skin, starting from the skin as the outermost layer, to the bones of the skull, blood vessels of the brain, and brain tissue as cranio-cerebral injuries. The degree of severity of head injury can be assessed with the Glasgow Coma Scale (GCS). Head injuries are divided into three according to the degree of mild, moderate, severe including, mild head injuries (13-15), moderate head injuries (9-12), and severe head injuries (3-8) (Chieregato et al., 2010).

Conventional diagnosis of head injury is more dependent on imaging examinations, especially CT scans of the head. An estimated 62 million head CT scans are performed each year in the US. Although the use of CT scans of the head has improved the diagnostic capabilities of head injuries, it has also raised concerns over unnecessary radiation exposure (Miyagawa et al., 2023). A head CT scan allegedly cannot detect all forms of head injury, namely diffuse axonal injury (DAI). Radiological examination that can detect the presence of DAI is by using MRI (Magnetic Resonance Imaging) but MRI itself is very expensive, requires a longer examination time and is not an examination of choice in acute head injuries (Hurley et al., 2004; Papa et al., 2012). The operative decision is usually determined based on the results of a CT scan of the head and monitoring of intracranial pressure. However, not all hospitals have fast access to imaging tests and intracranial pressure monitoring. Most hospitals in Indonesia, especially type C and D hospitals, do not have head CT scans. In addition, a head CT scan is a relatively expensive type of medical examination. This cost can be an obstacle for patients who do not have health insurance or who have insurance with limited coverage (Jain & Iverson, 2022).

Several criteria have been proposed to assess the severity of head injuries based on head CT scans, including the Marshall classification introduced in 1991, the Rotherdam score introduced in 2005 by reweighting the Marshall classification component and adding traumatic subarachnoid hemorrhage (tSAH) and bleeding. intraventricular, the Stockholm score in 2010 which uses midline shift as a follow-up variable and the Helsinki score in 2014 which is based on the components of the Marshall classification and the Rotterdam score, but also focuses more on the type of intracranial injury present. So far, no studies have shown the superiority of one criterion over the other, but similarities were found between systems where almost all of them used midline shift (MLS) and basal cistern parameters in assessing the severity of head injury. Midline shift and basal cisterns are known to act as indicators of increased intracranial pressure, brain edema and brainstem injury (Biuki et al., 2023; Thelin et al., 2017).

Recent clinical studies have explored the use of biomarkers as a new additional tool (Schiff et al., 2012). This biomarker originates from several cells in the central nervous system (CNS), can be examined quickly and repeatedly, and describes the structural damage associated with brain injury (Pelinka, 2004). Neuron Specific Enolase (NSE) is an alternative option which is considered more practical, cheaper, and does not require patient mobilization, especially for patients with severe head injuries who require total bed rest , to accompany clinical examinations and CT scans of the head (Sukorini et al., 2018).

Neuron-specific Enolase (NSE) is a glycolytic enzyme with a molecular weight of 78 kDa. NSE is found mostly in platelets and erythrocytes, and is released passively after cell damage and is not actively secreted into the serum. NSE is also found in the cytoplasm of neuronal cells, neuroendocrine cells and rare tumors associated with uptake such as small lung carcinoma, melanoma and neuroblastoma. NSE has a high sensitivity, persists, and improves rapidly after trauma, when compared with other markers of brain damage (Sukorini et al., 2018).

Neuron-Specific Enolase (NSE) can be increased due to hemolysis or CSF contamination with peripheral blood and is naturally expressed in erythrocytes. NSE was also found to be

increased in both ventricular cerebrospinal fluid (CSF) and peripheral serum, with a higher magnitude of increase corresponding to higher mortality and more severe scores on GCS for adults and children (Su et al., 2016).

Serum NSE levels were shown to be higher in patients with head injury and secondary hypoxia. A study of patients with severe diffuse axonal injury revealed a sensitivity of 100% and a specificity of 100% for predicting post-injury mortality at an NSE level of 950 ng/mL (Neher et al., 2014). The initial rise and peak levels of NSE are higher in non-survivors than in survivors of head injuries. Serum NSE levels were found to significantly correlate with injury severity in animal studies and elevated serum NSE levels correlated with the presence of intracerebral pathology on head CT scans (Mozaffari et al., 2021).

Based on the description above, the authors wanted to prove whether there is a picture between NSE serum levels and a CT scan of the head that describes the severity of a head injury. The researchers wanted to know the characteristics of head injured patients in the emergency room of RSUP Dr. M. Djamil Padang City, knowing the CT scan of the head and the value of serum Neuron-Specific Enolase (NSE) levels in head injured patients in the Emergency Room of RSUP Dr. M. Djamil Padang City, and determine the relationship between Neuron-Specific Enolase (NSE) serum levels and CT scan images of the head in head injured patients. The results of this study are expected to provide insight and information on health science developments as well as reference material for future researchers. The hypothesis in this study are:

1) H0: There is no relationship between NSE level and CT scan appearance; and
2) H1: There is a relationship between NSE levels and CT scan images.

METHODS

The type of research used in this research is analytic observational research, derived from quantitative approach. The study design in this study was a cross sectional which aims to describe the levels of Neuron Specific Enolase (NSE) serum with CT scan images of head injured patients at RSUP Dr. M. Djamil City of Padang. This research was conducted in the Emergency Room of RSUP Dr. M. Djamil, Padang City as the sampling location and the Biomedical Laboratory of the Faculty of Medicine, Andalas University as the research location and the research time starts from February to June 2023.

The target population in this study were all head injured patients in the emergency room of RSUP Dr. M. Djamil City of Padang. While the reachable population used in this study were all head injury patients who had just arrived (<24 hours) at the IGD Dr. M. Djamil Padang City in April and May 2023. The sampling technique used in this study was the consecutive sampling technique.

The type of data used in this research is primary data. The primary data in this study were data obtained directly from the results of examination and observation of NSE biomarkers in serum and observations of head CT scans in head injured patients. The data was collected through a questionnaire on the characteristics of the subject, the subject's medical history, and the results of a head CT scan. In addition, data was also collected by examining NSE biomarkers using the

ELISA Reader which was carried out at the Biomedical Laboratory, Faculty of Medicine, Andalas University. Then the data that has been obtained is analyzed by editing, coding, processing, and cleaning, followed by univariate and bivariate analysis.

RESULTS AND DISCUSSION

Characteristics of Respondents

This research was carried out on 30 head injured patients admitted to the emergency room of RSUP Dr. M. Djamil Padang in April-May 2023 with characteristics according to table 1.

Table 1. Characteristics of Head Injured Patients who Underwent Head CT Scan

Characteristics	Frequency (n)	Percent (%)
Age		
<20	4	13,3
20-29	9	30.0
30-39	5	16,7
40-49	4	13,3
≥50	8	26,7
Gender		
Man	25	83.3
Woman	5	16,7
CT scan image		
No Abnormalities	11	36,7
MLS <5 mm/Cisternic Constriction	16	53,3
MLS >5 mm/Sisterna Disappears	3	10.0
NSE levels		
Not elevated (<6.5 ng/ml)	13	43,3
Increased (≥6.5 ng/ml)	17	56,7
GCS		
Light (13-15)	18	60.0
Moderate (9-12)	6	20.0
Weight (3-8)	6	20.0

Table 1 shows that the majority of head injury patients who underwent head CT scans in the emergency room at M.Djamil Hospital Padang were in the age group of 20-29 years (30%) and were male (83.3%). The results of a CT scan of the head found that more than half of the respondents had MLS <5 mm / narrowing of the cisterns (53.3%). While the least percentage of patients with MLS > 5 mm/sisterna disappeared (10%). Then the patients who had no abnormalities on the CT scan were 36.7%. The results of the analysis showed that patients with NSE levels increased by 56.7% and patients with NSE levels did not increase by 43.3%. In the

GCS assessment, most of the patients were in the mild GCS group (13-15) which was 60%. While the percentage of patients with moderate and severe GCS is 20%.

Correlation between Serum NSE Levels and CT Scan Appearances

The results of the analysis of the relationship between serum NSE levels and head CT scan images in head injured patients at Dr. M. Djamil Padang can be seen in table 2.

Table 2. Relationship between Serum NSE Levels and Head CT Scan Images

NSE levels	CT scan image						P-values
	No Abnormalities		*MLS < 5 mm*		*MLS >5mm*		
	n	%	n	%	n	%	
Not increasing	6	54.5	6	37.5	1	33,3	0.635
Increase	5	45.5	10	62.5	2	66,7	
Total	11	100.0	16	100	3	100	

Table 2 shows that there were 11 patients with head CT scans showing no abnormalities, 6 patients (54.5%) of whom had NSE levels not increased (54.5%) and as many as 5 patients (45.5%) had elevated NSE levels. Then there were 16 patients with MLS <5 mm, 6 patients (37.5%) had non-increased NSE levels and as many as 10 patients (62.5%) had elevated NSE levels. Furthermore, of the 3 patients with MLS > 5 mm, 1 patient (33.3%) had non-increased NSE levels and as many as 2 patients (66.7%) had increased NSE levels. The results of the statistical test obtained p-value = 0.635, meaning that there was no relationship between NSE levels and CT scan images in head injured patients in the emergency department of M.Djamil Hospital, Padang.

Discussion

Based on table 1, it appears that head injury patients underwent a CT scan in the Emergency Room of RSUP Dr. M. Djamil Padang was mostly in the age group of 20-29 years (30%) and male (83.3%). This is in accordance with previous research conducted by Lecky FE et al. in 2021 in 18 countries which found that more than half (61.7%) of people with head injuries in various countries were under 65 years old. In addition, research conducted in Singapore in 2016 by Jing Zhong Wee *et al* also found that 68.2% of people with head injuries were under 60 years old. Research conducted by Ahmad Faried in 2017 in Bandung also found that almost all (96.1%) of head injury sufferers were under 60 years old and the majority (80.8%) were male. This can be explained because the majority of the causes of head injuries found in the emergency room are the result of traffic accidents, especially motorbikes, so they are found more in the productive age group than in the elderly or children group. Differences in incidence among different age and sex groups may indicate different predisposing factors. This is evidenced in part by the fact that substantially more young men are involved in high-risk activities such as motorized accidents and assault (Faried et al., 2017; Lecky et al., 2021; Prawiroharjo et al., 2020; Wee et al., 2016).

More than half (53.3%) of the head injured patients underwent a CT scan of the head in the Emergency Room of RSUP Dr. M. Djamil Padang shows a CT scan of the head in the form of a midline shift <5 mm/Cisternic Constriction and is most commonly classified as a mild head injury. These results are in accordance with research conducted by Prawiroharjo P at Cipto Mangunkusumo General Hospital in 2020, only a small proportion (19.1%) had head injuries with moderate to severe severity. This is explained by the fact that a greater midline shift is associated with a more severe head injury severity (GCS = 3-12) (Faried et al., 2017; Prawiroharjo et al., 2020).

The results of the analysis showed that patients with NSE levels increased by 56.7% and patients with NSE levels did not increase by 43.3%. Neuron Specific Enolase (NSE) is a marker that is quite useful in detecting neuronal damage and its level has been shown to increase in serum after head injury. In the study by Sun Y, et al, serum NSE levels in mild head injured patients averaged 13.12 $\pm$ 9.68, significantly higher than the control group. Higher serum NSE levels are associated with more severe head injury severity. The average level of NSE is higher in severe head injuries compared to moderate and mild head injuries. This is what makes it possible for almost half of the patients not to experience an increase in NSE levels, because most of the respondents have mild-moderate head injuries (Sun et al., 2021; Syafrita & Fitri, 2021).

Neuron specific enolase (NSE) is an enzyme involved in glycolysis of nerve cells and is specific for the brain. Several reports have found increased serum NSE levels to be correlated with an unfavorable outcome. Therefore, examination of biomarker levels in serum is expected to describe ongoing pathological conditions. High NSE serum levels in the acute phase are associated with poor outcome at 6 weeks after injury (Sun et al., 2021; Syafrita & Fitri, 2021).

Based on research that has been carried out through the Glasgow coma Scale (GCS) assessment, it can be seen that out of 30 samples of head injured patients at Dr. M. Djamil Padang City, the highest severity at the time of the study was minor head injuries, namely 18 people (60%). This is in line with a study conducted by Danang BU et al which showed that out of a total of 60 cases of head injury, the highest distribution of degrees of head injury was mild head injury, namely 28 cases (46.7%).

Correlation between Serum NSE Levels and CT Scan Appearances

Based on the results of statistical tests, it was found that p-value = 0.635, meaning that there was no relationship between NSE levels and CT scan images of the head in patients with head injuries in the emergency department of M.Djamil Hospital, Padang. There are several explanations that can be put forward. The acute increase in NSE is more related to the neurologic deficits acquired after head injury. Thus, compared with the CT scan findings of the acute phase of the head, elevated NSE levels were more significant as a predictor of sequelae after head injury. Higher levels of NSE are also more associated with higher mortality. Serum NSE level associated with mortality and poor outcome . However, there was no significant relationship between serum NSE levels and head CT scan findings in this study (Cheng et al., 2014; Sun et al., 2021).

NSE levels usually rise within the first 12 hours after injury and decrease over hours or days, with a half-life of approximately 24 hours. Secondary enhancement may occur in patients with poor clinical outcomes. Although NSE initially appeared to be a promising marker of injury severity because of a number of theoretical advantages, including its correlation with the number of affected neurons rather than glial cells and its high specificity for the brain, it has limitations. One of the main problems associated with its use as a marker of brain damage is the concentration of NSE which can be affected by hemolysis. Erythrocytes contain a large number of NSE. Hemolysis can cause a marked increase in NSE in the blood. Additionally, increased NSE has been documented in patients with multiple trauma without head injury. Thus, in cases of multiple trauma the results will be biased (Cheng et al., 2014; Sun et al., 2021).

In a study conducted by Mozafari et al ., it was found that in patients with mild head injuries who underwent a head CT scan, there was a significant difference in NSE levels in patients with the positive head CT scan group (2.7 ± 9.74 µg/L) and the positive head CT scan group (2.7 ± 9.74 µg/L) and the negative (4.23±1.33 µg/L) (P<0.0001) In addition, with a cut-off point of 6.97 µg/L, brain lesions could be detected with a sensitivity of 93.55% and a specificity of 100%. So that increased serum NSE levels can be used to detect brain lesions in mild head injuries. However, serum NSE levels cannot predict the extent of brain lesions that can be found on head CT scans (Mozafari et al., 2020).

Maraghi et al found a correlation between NSE level and CT change, although NSE at admission was higher in patients who worsened according to CT findings (means: 7.9, 9.6 and 20 in patients who improved, with the same CT findings). and worse), but not statistically significant (p = 0.15). NSE 48 hours after admission was significantly higher with worsening CT findings (means; 9, 11 and 30, each with p = 0.04) (El-Maraghi et al., 2013; Faried et al., 2017).

The timing of biomarker sampling in various studies varies widely. This allows the findings of different studies to vary. Some studies used only one sample at admission, while others sampled NSE more frequently. NSE shows low predictive power over time due to the longer half-life of NSE (Olivecrona et al., 2015; Thelin et al., 2016).

CONCLUSION

Head injury patients who underwent head CT scans at the M.Djamil Hospital Padang Emergency Room were found with the following characteristics: Age 20-29 years, male sex, CT scan of the head in the form of MLS<5mm/cistern narrowing, increased NSE level, severity mild head injury (GCS 13-15). In addition, there was an increase in NSE levels in head injured patients with MLS < 5 mm and MLS > 5 mm, but there was no statistical significance between NSE levels and head CT scan images in head injured patients in the Emergency Room of Dr. M. Djamil Padang.

This study was a cross-sectional study so that the NSE and CT scan levels were taken at the same time. Some literature explains that NSE levels actually function as predictors of outcome and have prognostic value in patients with head injuries. So further research is needed regarding the relationship between these two variables and the outcome of patients with head injuries. Further

research is needed regarding the association of serum NSE levels and CT scan images of head injured patients with outcomes in head injured patients and assessing changes in serum NSE levels in head injured patients with different experience times.

REFERENCE

Biuki, N. M., Talari, H. R., Tabatabaei, M. H., Abedzadeh - kalahroudi, M., Akbari, H., Esfahani, M. M., & Faghihi, R. (2023). Comparison of the predictive value of the Helsinki, Rotterdam, and Stockholm CT scores in predicting 6-month outcomes in patients with blunt traumatic brain injuries. *Chinese Journal of Traumatology*. https://doi.org/10.1016/j.cjtee.2023.04.002

Blazer, D. G., Bazarian, J., & Bogner, J. (2019). *Evaluation of the disability determination process for traumatic brain injury in veterans*. National Academies Press. https://doi.org/10.17226/25317

Cheng, F., Yuan, Q., Yang, J., Wang, W., & Liu, H. (2014). The prognostic value of serum neuron-specific enolase in traumatic brain injury: Systematic review and meta-analysis. *PLoS ONE*, *9*(9), e106680. https://doi.org/10.1371/journal.pone.0106680

Chieregato, A., Martino, C., Pransani, V., Nori, G., Russo, E., Noto, A., & Simini, B. (2010). Classification of a traumatic brain injury: The Glasgow Coma scale is not enough. *Acta Anaesthesiologica Scandinavica*, *54*(6), 696–702. https://doi.org/10.1111/j.1399-6576.2010.02234.x

El-Maraghi, S., Yehia, H., Hossam, H., Yehia, A., & Mowafy, H. (2013). The prognostic value of neuron specific enolase in head injury. *The Egyptian Journal of Critical Care Medicine*, *1*(1), 25–32. https://doi.org/10.1016/j.ejccm.2012.12.002

Faried, A., Bachani, A. M., Sendjaja, A. N., Hung, Y. W., & Arifin, M. Z. (2017a). Characteristics of moderate and severe traumatic brain injury of motorcycle crashes in Bandung, Indonesia. *World Neurosurgery*, *100*, 195–200. https://doi.org/10.1016/j.wneu.2016.12.133

Faried, A., Bachani, A. M., Sendjaja, A. N., Hung, Y. W., & Arifin, M. Z. (2017b). Characteristics of moderate and severe traumatic brain injury of motorcycle crashes in Bandung, Indonesia. *World Neurosurgery*, *100*, 195–200. https://doi.org/10.1016/j.wneu.2016.12.133

Hurley, R. A., McGowan, J. C., Arfanakis, K., & Taber, K. H. (2004). Traumatic axonal injury: Novel insights into evolution and identification. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(1), 1–7. https://doi.org/10.1176/jnp.16.1.1

Jain, S., & Iverson, L. M. (2022, June 21). *Glasgow Coma scale*. National Library of Medicine: National Center for Biotechnology Information.

Lecky, F. E., Otesile, O., Marincowitz, C., Majdan, M., Nieboer, D., Lingsma, H. F., Maegele, M., Citerio, G., Stocchetti, N., Steyerberg, E. W., Menon, D. K., & Maas, A. I. R. (2021). The burden of traumatic brain injury from low-energy falls among patients from 18 countries in the CENTER-TBI Registry: A comparative cohort study. *PLOS Medicine*, *18*(9), e1003761. https://doi.org/10.1371/journal.pmed.1003761

Miyagawa, T., Saga, M., Sasaki, M., Shimizu, M., & Yamaura, A. (2023). Statistical and machine learning approaches to predict the necessity for computed tomography in children with mild

traumatic brain injury. *PLoS ONE*, *18*(1 January). https://doi.org/10.1371/journal.pone.0278562

Mozafari, J., Motamed, H., Hanafi, M. G., & Fatehifar, B. (2020). The diagnostic value of neuron-specific enolase in children with mild blunt trauma requiring cranial CT scan. *Open Access Emergency Medicine*, *Volume 12*, 1–5. https://doi.org/10.2147/OAEM.S223179

Mozaffari, K., Dejam, D., Duong, C., Ding, K., French, A., Ng, E., Preet, K., Franks, A., Kwan, I., Phillips, H. W., Kim, D. Y., & Yang, I. (2021). Systematic review of serum biomarkers in traumatic brain injury. *Cureus*. https://doi.org/10.7759/cureus.17056

Neher, M. D., Keene, C. N., Rich, M. C., Moore, H. B., & Stahel, P. F. (2014). Serum biomarkers for traumatic brain injury. *Southern Medical Journal*, *107*(4), 248–255. https://doi.org/10.1097/SMJ.0000000000000086

Olivecrona, Z., Bobinski, L., & Koskinen, L.-O. D. (2015). Association of ICP, CPP, CT findings and S-100B and NSE in severe traumatic head injury. Prognostic value of the biomarkers. *Brain Injury*, *29*(4), 446–454. https://doi.org/10.3109/02699052.2014.989403

Papa, L., Lewis, L. M., Falk, J. L., Zhang, Z., Silvestri, S., Giordano, P., Brophy, G. M., Demery, J. A., Dixit, N. K., Ferguson, I., Liu, M. C., Mo, J., Akinyi, L., Schmid, K., Mondello, S., Robertson, C. S., Tortella, F. C., Hayes, R. L., & Wang, K. K. W. (2012). Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Annals of Emergency Medicine*, *59*(6), 471–483. https://doi.org/10.1016/j.annemergmed.2011.08.021

Pavlovic, D., Pekic, S., Stojanovic, M., & Popovic, V. (2019). Traumatic brain injury: neuropathological, neurocognitive and neurobehavioral sequelae. *Pituitary*, *22*(3), 270–282. https://doi.org/10.1007/s11102-019-00957-9

Pelinka, L. (2004). Serum markers of severe traumatic brain injury: Are they useful? *Indian Journal of Critical Care Medicine*, *8*(3).

Prawiroharjo, P., Pangeran, D., Supriawan, H., Lastri, D., Mayza, A., Zairinal, R. A., Dewi, A. R., Asmaniar, F., & Ramli, Y. (2020). Increasing traumatic brain injury incidence during COVID-19 pandemic in the Emergency Department of Cipto Mangunkusumo National General Hospital—A national referral hospital in Indonesia. *Neurology*, *95*(20 Supplement 1), S11.1-S11. https://doi.org/10.1212/01.wnl.0000719968.10580.81

Schiff, L., Hadker, N., Weiser, S., & Rausch, C. (2012). A literature review of the feasibility of glial fibrillary acidic protein as a biomarker for stroke and traumatic brain injury. *Molecular Diagnosis & Therapy*, *16*(2), 79–92. https://doi.org/10.1007/BF03256432

Su, Y. R. S., Veeravagu, A., & Grant, G. (2016). Neuroplasticity after traumatic brain injury. In *Translational Research in Traumatic Brain Injury* (pp. 186–201). CRC Press. https://doi.org/10.1201/b18959-13

Sukorini, U., Wulandari, I. S., Mulyono, B., & Pramusinto, H. (2018). Korelasi antara neuron-specific enolase serum dan glasgow coma scale di pasien cedera kepala. *Indonesian Journal of Clinical Pathology and Medical Laboratory*, *17*(1), 25–31. https://doi.org/10.24293/ijcpml.v17i1.1043

Sun, Y., Wang, S., Gan, S., Niu, X., Yin, B., Bai, G., Yang, X., Jia, X., Bai, L., & Zhang, M. (2021). Serum neuron-specific enolase levels associated with connectivity alterations in anterior default mode network after mild traumatic brain injury. *Journal of Neurotrauma*, *38*(11), 1495–1505. https://doi.org/10.1089/neu.2020.7372

Syafrita, Y., & Fitri, N. (2021). Analysis of neuron specific enolase serum levels in traumatic brain injury. *Bioscientia Medicina: Journal of Biomedicine and Translational Research*, *5*(4), 381–386.

Thelin, E. P., Jeppsson, E., Frostell, A., Svensson, M., Mondello, S., Bellander, B.-M., & Nelson, D. W. (2016). Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels, outcome, and extracranial injury severity. *Critical Care*, *20*(1), 285. https://doi.org/10.1186/s13054-016-1450-y

Thelin, E. P., Nelson, D. W., Vehviläinen, J., Nyström, H., Kivisaari, R., Siironen, J., Svensson, M., Skrifvars, M. B., Bellander, B.-M., & Raj, R. (2017). Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: An observational, multicenter study. *PLOS Medicine*, *14*(8), e1002368. https://doi.org/10.1371/journal.pmed.1002368

Wee, J., Yang, Y., Lee, Q., Cao, K., & Chong, C. (2016). Demographic profile and extent of healthcare resource utilisation of patients with severe traumatic brain injury: still a major public health problem. *Singapore Medical Journal*, *57*(09), 491–496. https://doi.org/10.11622/smedj.2015162