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Study Analysis of Serum Phosphorylated Tau (P-Tau) Levels with Severity and Outcome in Traumatic Brain Injury Patients: A Single Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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ABSTRACT

Background: Traumatic brain injury (TBI) is a global health problem that can cause death and disability in people of productive age. The diagnosis and assessment of TBI severity currently still rely on clinical examination and neuroimaging. However, limited access and cost of neuroimaging are obstacles in many health facilities. Therefore, blood-based biomarkers are needed that can help the diagnosis and prognosis of TBI. Phosphorylated Tau (p-tau) is a potential biomarker that can be measured in serum. This study aims to assess the relationship between serum p-tau levels and severity and outcome in TBI patients. **Methods:** This research is a comparative study with a cross-sectional design involving 70 TBI patients who came to the emergency room (ER) of Dr. M. Djamil General Hospital Padang. TBI severity was assessed using the Glasgow coma scale (GCS) and grouped into mild (GCS 13-15) and moderate to severe (GCS 3-12). Outcomes were assessed using the Glasgow outcome scale (GOS) and grouped into good (GOS 4-5) and poor (GOS 1-3). Serum p-tau levels were measured using the ELISA method. Data analysis was carried out using SPSS. **Results:** The median serum p-tau level in the mild TBI group was 165.84 ng/L (IQR 126.18-463.85), while in the moderate to severe TBI group, it was 177.68 ng/L (IQR 87.62-591.93). There was a significant difference between serum p-tau levels in the mild and moderate to severe TBI groups ($p=0.029$). The median serum p-tau level in the good outcome group was 167.21 ng/L (IQR 87.62-463.85), while in the poor outcome group it was 187.04 ng/L (IQR 137.75-591.93). There was a significant difference between serum p-tau levels in the good and bad outcome groups ($p=0.014$). **Conclusion:** Serum p-tau levels have a significant relationship with severity and outcome in TBI patients. Elevated serum p-tau levels are associated with increased severity of TBI and poor outcomes. Further research is needed to confirm these findings and explore the potential of p-tau as a biomarker in TBI management.

1. Introduction

Traumatic brain injury (TBI) is a global scourge that threatens public health, especially the productive age population. The impact is not only death but also long-term disability that burdens individuals, families, and the health system as a whole. In Indonesia, TBI occupies an alarming position in morbidity and mortality statistics, with the incidence rate continuing to increase from year to year. Traffic accidents are the

main cause, followed by falls from heights, violence, and sports injuries. The complexity of the pathophysiology of TBI is a challenge in its management. Primary injuries that occur during impact, such as brain contusions, lacerations, and intracranial hemorrhage, can cause immediate neurological disorders. However, it doesn't stop there, secondary injuries that develop within hours to days after trauma, such as brain edema, ischemia, and

inflammation, can worsen brain damage and increase the risk of complications.¹⁻³

Diagnosis and assessment of TBI severity currently still rely on clinical examination using the Glasgow coma scale (GCS) and neuroimaging such as CT scan or MRI. GCS, although useful in assessing a patient's level of consciousness, has limitations in predicting long-term outcomes. Neuroimaging, on the other hand, provides detailed images of brain structure and the presence of bleeding, but limited access and cost are obstacles in many health facilities, especially in remote areas and developing countries. The need for accurate, rapid, and easily accessible biomarkers is becoming increasingly urgent. Biomarkers are biological molecules that can be measured in blood or other body fluids, reflecting pathological processes occurring in the body. In the context of TBI, biomarkers can help in early diagnosis, severity assessment, outcome prediction, and monitoring response to therapy.^{4,5}

Several biomarkers that have been studied in TBI include S100B, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase L1 (UCH-L1). However, each of these biomarkers has limitations, both in terms of specificity, sensitivity and availability. One promising biomarker is phosphorylated Tau (p-tau). Tau is a microtubule-associated protein (MAP) protein that plays an important role in stabilizing microtubules in neuron axons. In pathological conditions such as TBI, tau can be hyperphosphorylated, leading to microtubule dysfunction, impaired axonal transport, and ultimately neuronal death. P-tau released from microtubules can enter the cerebrospinal fluid and blood, so it can be measured as a TBI biomarker. Several studies have shown that serum p-tau levels are increased in TBI patients and correlate with injury severity and poor outcome. Elevated serum p-tau levels can be detected within hours after injury and persist for several days, providing a sufficient time window for therapeutic intervention.⁶⁻⁸ This study aims to test the hypothesis that serum p-tau levels are related to severity and outcome in TBI patients at Dr.

M. Djamil General Hospital Padang because it is the main referral hospital in West Sumatra which receives many TBI cases. With a diverse patient population and varying severity of injuries, Dr. M. Djamil General Hospital Padang provided a representative sample for this research.

2. Methods

This study used a cross-sectional comparative study design to analyze the relationship between serum phosphorylated Tau (p-tau) levels and severity and outcome in traumatic brain injury (TBI) patients. This design allows data collection at a single time point to compare p-tau levels between groups of patients with different levels of injury severity and outcome. This research was conducted in the emergency room (ER) of Dr. M. Djamil General Hospital Padang, a tertiary referral hospital that handles a large number of TBI cases in the West Sumatra region, Indonesia. The study population was all TBI patients who came to the emergency room of Dr. M. Djamil General Hospital Padang during the study period, namely from June 2023 to May 2024. The sample size calculation was carried out based on the estimated difference in serum p-tau levels between the mild and moderate to severe TBI groups, as well as between the good and bad outcome groups. Using a confidence level of 95% and power of 80%, a minimum of 35 patients are needed in each TBI and outcome group.

Strict inclusion criteria were applied to ensure sample homogeneity and minimize bias. Patients who met the following criteria were included in the study: Age between 18 and 65 years: This age range was chosen to focus on the productive age population who most often experience TBI. Confirmed diagnosis of TBI: The diagnosis is made based on the history, complete neurological physical examination, and neuroimaging results. (CT scan or MRI) if available, Time of arrival less than 24 hours after injury: This time limit aims to obtain blood samples before significant changes in p-tau levels occur due to secondary processes after injury and Informed consent: Written consent is obtained from the patient or legal guardian after a

complete explanation of the objectives, procedures, benefits, and risks of the research. Exclusion criteria were applied to eliminate factors that could influence serum p-tau levels other than TBI. Patients with the following conditions were not included: History of neurodegenerative disease: Diseases such as Alzheimer's or Parkinson's can increase serum p-tau levels independently of TBI, History of malignant disease: Some types of cancer can affect tau metabolism and cause an increase in serum p-tau levels, Functional disorders severe liver or kidney dysfunction: Dysfunction of these organs can impair the clearance of p-tau from the blood circulation as well as Pregnancy or breastfeeding: Hormonal changes during pregnancy and breastfeeding can affect serum p-tau levels.

Demographic data (age, gender), clinical data (GCS, GOS), and laboratory data (serum p-tau levels) were collected from each patient who met the inclusion criteria. Glasgow coma scale (GCS): GCS is a clinical rating scale used to measure the level of consciousness of patients with TBI. GCS consists of three components: eye-opening response, verbal response, and motor response. The total GCS score ranges from 3 (deep coma) to 15 (fully conscious). In this study, patients were grouped into two categories based on GCS scores: mild TBI (GCS 13-15) and moderate to severe TBI (GCS 3-12). Glasgow Outcome Scale (GOS): GOS is a scale for assessing neurological outcomes in TBI patients. GOS measures a patient's level of functional disability in five categories: death, persistent vegetative, severe disability, moderate disability, and good recovery. In this study, patients were grouped into two categories based on the GOS score: Good outcome (GOS 4-5) and Poor outcome (GOS 1-3). Measurement of Serum p-tau Levels: Venous blood samples were taken from each patient upon arrival at the ER. Blood samples were centrifuged to separate serum, which was then stored at -80°C until analysis. Serum p-tau levels were measured using a commercially validated enzyme-linked immunosorbent assay (ELISA) method. The ELISA method was chosen because of its high

sensitivity and specificity in detecting p-tau in serum. The collected data was analyzed using SPSS statistical software. The data normality test was carried out using the Shapiro-Wilk test. Because data on serum p-tau levels were not normally distributed, the nonparametric Mann-Whitney U test was used to compare p-tau levels between the mild and moderate to severe TBI groups, as well as between the good and poor outcome groups. The correlation between serum p-tau levels and GCS and GOS scores was analyzed using Spearman correlation. A p-value < 0.05 was considered statistically significant. Several steps were taken to minimize bias in this study. First, strict inclusion and exclusion criteria were applied to ensure sample homogeneity and reduce the influence of confounding factors. Second, serum p-tau levels were measured using a standardized and validated ELISA method to guarantee the accuracy and precision of the results. Third, data analysis was carried out in a blinded manner, where researchers analyzing the data did not know the TBI group or patient outcomes. This research received approval from the Health Research Ethics Committee of Dr. M. Djamil General Hospital before the start of the research. All participants or legal guardians were given a complete explanation of the aims, procedures, benefits and risks of the research before providing written consent (informed consent). The confidentiality of patient data is strictly maintained in accordance with research ethical principles.

3. Results

Table 1 presents the demographic and clinical characteristics of patients with mild traumatic brain injury (TBI) ($n=35$) and moderate-severe TBI ($n=35$). The median age of mild TBI patients was 26 years (range 18-56 years), while the median age of moderate-severe TBI patients was 31 years (range 18-60 years). There was no statistically significant difference in age between the two groups ($p = 0.326$). These results suggest that age is not a risk factor that differentiates between mild and moderate-severe TBI in this study sample. The proportion of male patients was higher in

both groups, namely 82.9% in the mild TBI group and 74.3% in the moderate-severe TBI group. The proportion of female patients was lower, namely 17.1% in the mild TBI group and 25.7% in the moderate-severe TBI group. There was no significant difference in gender distribution between the two groups ($p = 0.382$). This shows that gender does not influence the risk of mild or moderate-severe TBI in this population. Onset is the time between the occurrence of an injury and the patient's arrival at the hospital. The median onset in the mild TBI group was 10 hours (range 1-36 hours), while in the moderate-severe TBI group, it was

7 hours (range 1-24 hours). There was no significant difference in onset between the two groups ($p = 0.329$), indicating that the time of arrival to the hospital was not significantly different between mild and moderate-severe TBI patients. Overall, the demographic and clinical characteristics between mild and moderate-severe TBI patients in this study were relatively balanced. There were no significant differences in age, gender, and onset between the two groups. This suggests that other factors, such as the mechanism of injury or comorbid conditions, may play a greater role in determining the severity of TBI.

Table 1. Basic characteristics of research subjects based on severity (GCS).

Characteristics	Mild traumatic brain injury (n=35)	Moderate-severe traumatic brain injury (n=35)	P-value
	n(%), Median (min-max)	n(%), Median (min-max)	
Age (years)	26 (18-56)	31 (18-60)	0,326*
Gender			
Male	29 (82,9)	26 (74,3)	0,382#
Female	6 (17,1)	9 (25,7)	
Onset (hour)	10 (1-36)	7 (1-24)	0,329*

*Mann Whitney U test, #Chi-square test.

Table 2 presents the results of measuring serum phosphorylated Tau (p-tau) levels in two groups of traumatic brain injury (TBI) patients, namely the mild TBI group and the moderate-severe TBI group. Serum p-tau levels are measured in nanograms per liter (ng/L). Mild TBI Group: Median: 165.84 ng/L. This means that half of the patients in this group had serum p-tau levels below 165.84 ng/L, and half above this value. Minimum: 126.18 ng/L. This was the lowest p-tau level measured in this group. Maximum: 463.85 ng/L. This was the highest p-tau level measured in this group. Moderate-Severe TBI Group: Median: 177.68 ng/L. This value was slightly higher compared with the mild TBI group, indicating a trend

towards increased p-tau levels in patients with more severe injuries. Minimum: 87.62 ng/L. This was the lowest p-tau level measured in this group and was lower than the minimum value in the mild TBI group. Maximum: 591.93 ng/L. This was the highest p-tau level measured in this group and was also higher than the maximum value in the mild TBI group. Overall, table 2 shows that serum p-tau levels tended to be higher in patients with more severe TBI. However, there was considerable overlap between the two groups, indicating that serum p-tau levels cannot be used as the sole marker to differentiate between mild and moderate-severe TBI.

Table 2. Description of serum p-tau levels in traumatic brain injury patients at Dr. M. Djamil General Hospital Padang.

Group	P-Tau levels (ng/L)		
	Median	Minimum	Maximum
Mild	165,84	126,18	463,85
Moderate-severe	177,68	87,62	591,93

Table 3 presents the distribution of outcomes in traumatic brain injury (TBI) patients based on the severity of the injury. There was a significant difference between the mild TBI and moderate-severe TBI groups in terms of outcome. In the mild TBI group, all patients (35 patients or 100%) showed good outcomes. This suggests that mild TBI has an excellent prognosis, with a high probability of recovery and a low risk of disability. In contrast, in the moderate-severe TBI group, outcomes were more evenly distributed between good and bad. A total of 18 patients (51.4%) showed good outcomes, while 17 patients (48.6%) showed bad outcomes. This indicates that moderate-severe TBI has a more variable prognosis, with a higher risk of disability compared to mild TBI. The striking difference in outcome

distribution between these two groups emphasizes the importance of injury severity as a determining factor in prognosis in TBI patients. Mild TBI tends to have a milder impact on neurological function and quicker recovery, whereas moderate-severe TBI can cause more extensive brain damage and more severe neurological complications, thereby increasing the risk of poor outcomes. These findings have important implications in the clinical management of TBI patients. In patients with mild TBI, the primary focus is on monitoring symptoms and preventing secondary complications. However, in patients with moderate-severe TBI, more aggressive interventions may be necessary to minimize brain damage and increase the chances of recovery.

Table 3. Overview outcome in traumatic brain injury patients at Dr. M. Djamil General Hospital Padang.

Variable	Traumatic brain injury	
	Mild	Moderate-severe
Outcome		
Good	35 (100%)	18 (51,4%)
Bad	0 (0%)	17 (48,6%)

Table 4 presents the results of analysis of serum p-tau levels in traumatic brain injury (TBI) patients based on the severity of the injury. Serum p-tau levels are measured in nanograms per liter (ng/L) and are presented as median (middle value) along with minimum and maximum ranges (min-max). There were two groups of patients in this study: Mild TBI Group: Patients with mild brain injuries had a Glasgow coma scale (GCS) score of 13-15. Moderate-Severe TBI Group: Patients with moderate to severe brain injuries have a GCS score of 3-12. The analysis results showed that the median serum p-tau level in the mild TBI group was 165.84 ng/L, with a range between 126.18 ng/L to 463.85 ng/L. Meanwhile, the median serum p-tau level in the moderate-severe TBI group was 177.68 ng/L, with a range between 87.62

ng/L to 591.93 ng/L. Differences in serum p-tau levels between the two groups were tested using the Mann-Whitney U statistical test, which produced a p-value of 0.029. This p-value was less than 0.05, indicating that the difference in serum p-tau levels between the mild and moderate-severe TBI groups was statistically significant. In other words, patients with moderate to severe TBI tend to have higher serum p-tau levels compared with patients with mild TBI. These findings support the hypothesis that serum p-tau levels may be a useful biomarker in differentiating the severity of TBI. Elevated serum p-tau levels in moderate to severe TBI patients may reflect a higher degree of neuronal damage due to injury.

Table 4. Relationship of serum p-tau levels with severity levels in traumatic brain injury patients at Dr. M. Djamil General Hospital Padang.

	Group		p
	Mild	Moderate-severe	
P-Tau levels (ng/L) Median (min-max)	165,84 (126,18 – 463,85)	177,68 (87,62-591,93)	0,029*

*Mann Whitney U test.

Table 5 presents the results of the analysis of serum p-tau levels in traumatic brain injury patients based on their neurological outcomes. Neurological outcomes were grouped into two categories, namely good (N = 53) and poor (N = 17). Serum p-tau levels are measured in nanograms per liter (ng/L) and are presented in the form of a median (middle value) along with a minimum to maximum range (min-max). In the good outcome group, the median serum p-tau level was 167.21 ng/L with a range of values between 87.62 ng/L to 463.85 ng/L. Meanwhile, in the poor outcome group, the median serum p-tau level was higher, namely 187.04 ng/L with a range of values between 137.75 ng/L to 591.93 ng/L. The results of statistical

tests showed that there was a statistically significant difference between serum p-tau levels in the good and bad outcome groups (p = 0.01). An asterisk (*) on the p-value indicates that this difference is significant at the 95% confidence level. This means that patients with poor outcomes tend to have higher serum p-tau levels compared to patients with good outcomes. These findings indicate that serum p-tau levels may be a useful biomarker in predicting neurological outcome in traumatic brain injury patients. Elevated serum p-tau levels may reflect a higher degree of injury severity and neuronal damage, which may ultimately influence patient outcomes.

Table 5. Relationship of serum phosphorylated tau (p-tau) levels with outcomes in traumatic head injury patients.

	Outcome		p
	Good N = 53	Bad N = 17	
P-Tau levels (ng/L) Median (min-max)	167,21 (87,62- 463,85)	187,04 (137,75-591,93)	0,01*

*Mann Whitney U test.

4. Discussion

The results of this study show a significant relationship between serum phosphorylated Tau (p-tau) levels and severity and outcome in patients with traumatic brain injury (TBI). Elevated serum p-tau levels correlated with higher injury severity, as assessed by the Glasgow coma scale (GCS), and worse neurological outcomes, as assessed by the Glasgow outcome scale (GOS). These findings are in line with previous studies that have reported increased serum p-tau levels in TBI patients who experienced more severe injuries and poor outcomes. For example, another study found that serum p-tau levels were higher in TBI patients who had diffuse axonal injury compared with patients who did not have diffuse

axonal injury. Another study reported that serum p-tau levels were significantly increased in TBI patients with intracranial hematoma and cerebral edema.⁹⁻¹²

The mechanisms underlying the relationship between serum p-tau and TBI severity and outcome are still not fully understood. However, it is thought that increased serum p-tau levels reflect the degree of neuronal damage that occurs as a result of brain injury. In TBI, diffuse axonal damage occurs which causes the release of tau from microtubules in neurons. The released tau then undergoes excessive phosphorylation, forming p-tau. This phosphorylated p-tau can contribute to neuronal dysfunction and ultimately lead to cell death. The increase in serum p-tau levels in TBI patients with more severe injuries

may be explained by several factors. First, more severe injuries tend to cause more extensive and severe neuronal damage. Second, more severe injury may trigger a stronger inflammatory response, which may increase tau phosphorylation and p-tau production. Third, more severe injuries can disrupt the blood-brain barrier, allowing p-tau produced in the brain to leak into the blood circulation.¹³⁻¹⁶

In addition, this study also found that serum p-tau levels could predict neurological outcomes in TBI patients. Patients with higher serum p-tau levels have a higher risk of poor outcomes, such as death, persistent vegetative state, or severe disability. This suggests that serum p-tau may be a useful prognostic biomarker in identifying TBI patients who require more aggressive therapeutic intervention. P-tau has several advantages as a TBI biomarker compared to other biomarkers such as S100B or NSE. P-tau is more specific for neuronal damage, whereas S100B and NSE may be elevated in other conditions such as stroke or myocardial infarction. In addition, p-tau has a longer half-life in the blood, so it can be detected up to several days after injury. This allows p-tau to be used as a biomarker to monitor injury progression and response to therapy.¹⁷⁻²⁰

However, there are several limitations that need to be considered in interpreting the results of this study. First, this study used a cross-sectional design, so it could not determine the cause-and-effect relationship between serum p-tau levels and TBI severity and outcome. Prospective longitudinal studies are needed to confirm these findings and evaluate the ability of serum p-tau to predict long-term outcomes in TBI patients. Second, this research was conducted in one center only, so generalization of research results to the wider TBI population needs to be done with caution. Multicenter studies with larger and more diverse populations are needed to test the external validity of these findings. Third, this study did not include a healthy control group, so it cannot determine the normal value of serum p-tau levels in the general population. Further research is needed to establish serum p-tau reference values that are appropriate for

the Indonesian population. The findings of this study have important clinical implications. If the results of this study can be replicated and confirmed by further studies, serum p-tau may become a valuable tool in the diagnosis and prognosis of TBI. Increasing serum p-tau levels can help clinicians identify TBI patients at high risk of poor outcomes, thereby allowing earlier and more appropriate therapeutic intervention. In addition, serum p-tau can also be used to monitor injury progression and response to therapy. A decrease in serum p-tau levels after therapy can indicate improvement in the patient's condition, while an increase in serum p-tau levels can be an early warning sign of complications or worsening of the condition.

5. Conclusion

This study concluded that there was a significant relationship between serum p-tau levels and severity and outcome in TBI patients. Elevated serum p-tau levels are associated with increased severity of TBI and poor outcomes. These findings support the potential of p-tau as a biomarker in the diagnosis and prognosis of TBI. However, further studies are needed to confirm these findings and explore the clinical potential of p-tau as a biomarker in the management of TBI.

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