

The Relationship Between Blood Levels of Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) Protein and the Severity of Traumatic Brain Injury Based on the Glasgow Coma Scale and Rotterdam CT Score

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ABSTRACT

Objective: Traumatic brain injury (TBI) is a leading cause of disability and death worldwide, with an estimated 64-74 million cases annually. The current gold standard for diagnosis is a computed tomography (CT) scan, which has limitations such as access, cost, and radiation risk. Therefore, a simple, accessible, and safe diagnostic modality is needed, one of which is biomarker examination. This study aims to establish the relationship between blood levels of the biomarker ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and the severity of TBI based on the Glasgow Coma Scale (GCS) and Rotterdam CT score. **Material and Methods:** This observational analytic study with a cross-sectional design involved 41 samples aged 18-50 years who presented to the Emergency Department of Dr. Soetomo General Hospital, Surabaya, within 3-24 hours of the incident. UCH-L1 levels were measured from blood samples using the ELISA method, and the data on UCH-L1, GCS, and Rotterdam CT scores were analyzed with SPSS 29. **Results:** The mean UCH-L1 level was 0.522 ± 0.592 , with a cutoff value of > 0.2057 , indicating moderate to severe TBI if UCH-L1 levels exceeded 0.2057. Spearman's test and correlation coefficient analysis showed a strong relationship between UCH-L1 levels and Rotterdam CT score ($p < 0.05$), as well as between UCH-L1 levels and TBI severity based on GCS ($p < 0.05$). The cutoff value for Rotterdam CT score was > 2 , indicating moderate to severe TBI if the score exceeded 2. **Conclusion:** Serum UCH-L1 levels are significantly associated with the severity of TBI based on GCS and Rotterdam CT score.

Keywords: Traumatic brain injury, UCH-L1, Rotterdam CT score, Glasgow Coma Scale.

INTRODUCTION

Traumatic brain injury (TBI) disrupts brain function and can be caused by impact or penetrating injuries. In 2019, the CDC recorded 223,135 hospitalizations related to TBI in the United States.¹ In Asia, the incidence of TBI was 344 per 100,000 population in 2013.² According to Riseskdas 2018, head injuries accounted for 11.79% of 1,678 trauma cases in Indonesia.³ Dr. R. Sosodoro Djatikoesoemo General Hospital in Bojonegoro reported 800 TBI patients from 2020 to 2022.⁴ Dr. Soetomo General Hospital in Surabaya reported 1,178 TBI cases per year with a mortality rate of 6.17-11.22% between 2009 and 2013.²

Acute TBI patients require rapid evaluation and stabilization. Initial and periodic evaluations using the Glasgow Coma Scale (GCS) help determine therapy and prognosis.⁵ A non-contrast CT scan is the gold standard for initial imaging in patients with decreased consciousness, as it reveals intracranial pathologies requiring urgent surgical intervention.^{6,7}

Deciding to perform a CT scan on head injury patients is challenging due to limitations such as radiation exposure, patient transport requirements, high costs, and the time and effort needed, which

can cause delays. Therefore, a simple, accessible, and safe diagnostic modality for TBI patients is needed. Biomarker examination is one alternative, with sensitive and specific biomarkers being crucial for disease diagnosis and prognosis.^{8,9}

Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) is a protein biomarker extensively studied in TBI. UCH-L1 is abundant in neuronal cell bodies in the brain (5% of cytoplasmic protein) and is present in small amounts in gonadal organs and certain cancers like pancreatic, colorectal, and breast cancers.¹⁰ UCH-L1 is a promising candidate biomarker due to its abundance in nerve cells and its role in maintaining neural structure.¹¹ Damaged nerve cells release UCH-L1 into the cerebrospinal fluid, and it can be detected in the systemic circulation.⁸

Previous studies have shown that UCH-L1 levels significantly increase in moderate to severe TBI patients compared to healthy individuals and those with mild TBI.¹¹ UCH-L1 also has high accuracy in predicting CT scan findings across all GCS levels.^{8,12,13} Based on this, researchers will evaluate the relationship between blood UCH-L1 levels and TBI severity using GCS and Rotterdam CT Score.

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MATERIAL AND METHODS

Study Design and Subject Recruitment

This study is a diagnostic test with a cross-sectional design aimed at determining the relationship between blood UCH-L1 levels and the severity of traumatic brain injury (TBI) based on GCS and Rotterdam CT Score in TBI patients after the primary survey. The sample consisted of all TBI patients presenting to the Emergency Department of Dr. Soetomo General Academic Hospital who met the inclusion and exclusion criteria, totaling 41 subjects. TBI patients within 3-24 hours were evaluated, blood samples were taken to measure UCH-L1 levels using ELISA, and GCS was assessed to determine severity (mild, moderate, severe). Patients also underwent CT scans to assess brain structure using the Rotterdam CT Score, categorized from scores 1 to 6. Data from each category were analyzed for correlation with blood UCH-L1 levels.

Statistical Analysis

Collected data were processed using the statistical software SPSS 29. Data distribution was first tested for normality using the Shapiro-Wilk test. If data were normally distributed, Pearson's correlation was used; if not, Spearman's rho was applied.

RESULTS

Characteristics of Study Subjects

The demographic characteristics of this study are divided into general and clinical. General characteristics include gender, age, and ethnicity,

while clinical characteristics include comorbidities, trauma, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2), temperature, and systolic and diastolic blood pressure. The following table presents demographic results in frequency, percentage, mean, and standard deviation (SD):

Table 1 shows the distribution of general characteristics for 41 samples: 28 (68.3%) males and 13 (31.7%) females. Ages ranged from 18 to 50 years with a mean of 35.63 ± 13.26 years. The majority of samples were Javanese (35 or 85.4%), while 6 (14.6%) were Madurese.

The distribution of clinical characteristics shows that 15 samples (36.6%) had comorbidities, while 26 (63.4%) did not. Comorbidities included hypertension (12 or 29.3%), type 2 diabetes mellitus (2 or 4.9%), and grade 1 obesity (4 or 9.8%). Trauma was due to traffic accidents in 36 samples (87.8%) and falls in 5 samples (12.2%). The mean MAP was 93.22 ± 11.81 , HR 92.51 ± 14.71 , SpO2 98.54 ± 0.50 , body temperature 36.67 ± 0.21 , systolic blood pressure 129.66 ± 15.69 , and diastolic blood pressure 76.12 ± 9.49 .

Overview of UCH-L1 Levels

UCH-L1 levels were measured in the blood of TBI patients within 3-24 hours using the ELISA method. The data, being ratio-based, required normality testing using the Shapiro-Wilk test due to the sample size of 41 (<50 samples). This normality test determines whether parametric or non-parametric methods will be used for further analysis. Table 2 describes UCH-L1 levels and normality test results.

Table 2 shows UCH-L1 levels in 41 samples, ranging from 0.0827 to 2,659, with a mean and standard deviation of 0.522 ± 0.592 . The

Table 1. Distribution of Demographic Characteristics.

Characteristics	N (%)	Range	Mean \pm SD	p-value normality*
General Characteristics				
Gender				
Male	28 (68.3%)	-	-	-
Female	13 (31.7%)	-	-	-
Age	41 (100%)	18 - 50	35.63 ± 13.26	0.001
Ethnicity				
Javanese	35 (85.4%)	-	-	-
Madura	6 (14.6%)	-	-	-
Clinical Characteristics				
Comorbidities				
None	26 (63.4%)	-	-	-
Present	15 (36.6%)	-	-	-
Hypertension (HT)	12 (29.3%)	-	-	-
Type 2 Diabetes Mellitus (DM)	2 (4.9%)	-	-	-
Grade 1 Obesity	4 (9.8%)	-	-	-
Trauma				
Traffic Accident (TA)	36 (87.8%)	-	-	-
Fall	5 (12.2%)	-	-	-
MAP	41 (100%)	68 - 116	93.22 ± 11.81	0.296
HR	41 (100%)	67 - 116	92.51 ± 14.71	0.060
SpO2	41 (100%)	98 - 99	98.54 ± 0.50	0.001
Temperature	41 (100%)	36.2 - 36.9	36.67 ± 0.21	0.001
Systolic BP	41 (100%)	101 - 170	129.66 ± 15.69	0.272
Diastolic BP	41 (100%)	50 - 90	76.12 ± 9.49	0.050

*Data is considered normally distributed if the p-value > 0.05

Table 2. Descriptive Levels of UCH-L1 and Normality test.

	N	Range	Mean \pm SD	p-value normality*
UCH-L1 Levels	41	0.0827 - 2,659	0.522 ± 0.592	0.001

Table 3. GCS Description.

Grouping of COT based on GCS	N (%)
Range (Mean ± Sd)	4-15 (8.76 ± 3.48)
Mild (13-15)	8 (19.5%)
Moderate (9-12)	13 (31.7%)
Severe (3-8)	20 (48.8%)

Table 4. Relationship Test Between UCH-L1 Levels and Rotterdam CT Score.

	N	r	p-value	Information
UCH-L1 Levels with Rotterdam CT Score	41	0.661	0.001	Related

*considered related if the p-value < 0.05

Table 5. Relationship Test Between UCH-L1 Levels and GCS.

COT Grouping Based on GCS	N	UCH-L1 Levels		r	p-value
		Range	Mean ± SD		
Mild (13-15)	8	0.0827 – 0.3212	0.1866 ± 0.0668	0.705	0.001
Moderate (9-12)	13	0.2253 – 1,0279	0.3575 ± 0.2556		
Severe (3-8)	20	0.2144 – 2,6597	0.7624 ± 0.7535		

*Considered different if the p-value < 0.05

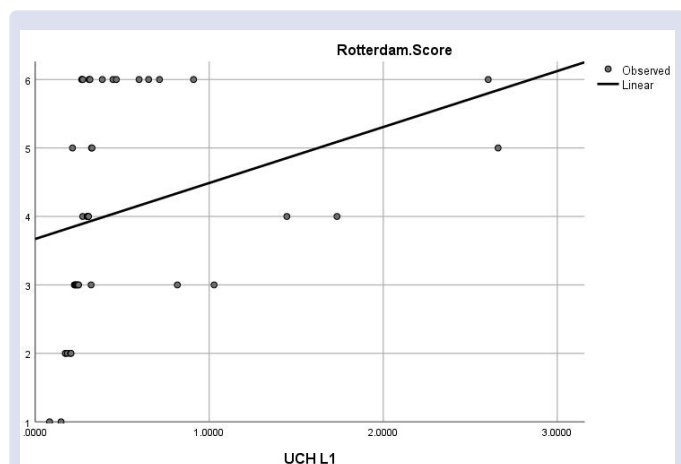


Figure 1. Scatterplot of UCH-L1 levels and Rotterdam CT score.

Shapiro-Wilk normality test resulted in a p-value of 0.001, indicating that UCH-L1 levels are not normally distributed, thus requiring non-parametric methods for further analysis.

Overview of GCS

The Glasgow Coma Scale (GCS) measures the consciousness level of TBI patients to assess injury severity within 3-24 hours based on eye-opening, verbal, and motor responses, scored between 3 and 15. These scores are then categorized as ordinal data: scores 3-8 indicate severe TBI, 9-12 indicate moderate TBI, and 13-15 indicate mild TBI. Table 3 presents the GCS distribution:

Table 3 shows GCS scores for 41 samples ranging from 4 to 15, with a mean of 8.76 ± 3.48. The frequency of GCS for mild TBI was 8 (19.5%), moderate TBI 13 (31.7%), and severe TBI 20 (48.8%).

Analysis of the Relationship Test Between UCH-L1 Levels and Rotterdam CT Score

The relationship between UCH-L1 levels and the Rotterdam CT Score was tested using the Spearman test because both datasets were not normally distributed. The table below shows the results of the UCH-L1 levels and Rotterdam CT Score relationship test:

Table 4 shows the Spearman test results for the relationship between UCH-L1 levels and Rotterdam CT Score with a p-value of 0.001 (<0.05), indicating a significant relationship. The correlation coefficient (r) of 0.661 indicates a positive and direct relationship, meaning that higher UCH-L1 levels correspond to higher Rotterdam CT Scores, with a relationship strength categorized as strong at 0.661.

Analysis of the Relationship Test Between UCH-L1 Levels and TBI Grouping Based on GCS

The relationship between UCH-L1 levels and GCS was tested using the Spearman test because UCH-L1 data were not normally distributed, and GCS is ordinal. The table below shows the results of this test:

Table 5 shows the mean and standard deviation of UCH-L1 levels based on GCS: mild TBI 0.1866 ± 0.0668, moderate TBI 0.3575 ± 0.2556, and severe TBI 0.7624 ± 0.7535. The Spearman test showed a p-value of 0.001 (<0.05), indicating a significant relationship between UCH-L1 levels and TBI severity grouping based on GCS.

DISCUSSION

This study involved 41 subjects, with a higher proportion of males (68.3%) compared to females (31.7%). This aligns with research indicating that males have a higher prevalence of traumatic brain injury (TBI) compared to females, with a ratio of 2:1.¹⁴ Another study on TBI also found that the prevalence among males in the general population is 16.7%, compared to only 8.5% among females.¹⁵

Overview of UCH-L1 Levels

Ubiquitin Carboxyterminal Hydrolase L1 (UCH-L1) is a proposed biomarker for traumatic brain injury (TBI). UCH-L1 is a cytoplasmic deubiquitinating enzyme specific to neurons and is highly abundant in the brain.^{16,17} Studies have shown that UCH-L1 levels significantly increase in the serum of TBI patients, including children, within the first 24 hours after injury.^{16,18} The mechanism by which UCH-L1 is transported from the brain to the circulation is not well understood, but it is hypothesized that UCH-L1 effluxes into the extracellular fluid during neuronal injury, leaks through the damaged blood-brain barrier, and equilibrates in the blood.¹⁸

Overview of GCS

The Glasgow Coma Scale (GCS) is used to assess the level of consciousness and severity of TBI based on eye, verbal, and motor responses. This scale provides prognostic information and guides treatment, making it a crucial examination in emergency and intensive care settings.^{5,19,20} Patients with GCS scores of 13-15 (mild TBI) have a good prognosis and low mortality (0.1%). Patients with GCS scores below 13 (moderate to severe TBI) have a poor prognosis with a 30% mortality rate, increasing to 50% for GCS scores below 9.^{21,22} This study showed a mean GCS score of 8.76 ± 3.48, with 19.5% mild TBI, 31.7% moderate TBI, and 48.8% severe TBI.

Analysis of the Relationship Test Between UCH-L1 Levels and Rotterdam CT Score

Previous studies have indicated that blood biomarkers can detect intracranial injuries post-TBI, potentially reducing unnecessary head CT scans. Proteins like UCH-L1 and GFAP are promising for brain injury diagnostics. Earlier studies demonstrated that UCH-L1 and GFAP can predict intracranial injuries on CT scans, though limited by small sample sizes, cut-off biases, and varied sampling times.¹²

This study found a significant relationship between blood UCH-L1 levels and Rotterdam CT scores; higher UCH-L1 levels correlated with higher Rotterdam CT scores. Out of 1920 TBI patients with GCS scores of 14-15, 666 had negative CT scan findings. High-sensitivity blood

biomarker tests with high negative predictive value (NPV) could avoid CT scans in about one-third of these patients. Clinically, UCH-L1 testing is expected to reduce CT scan usage and detect intracranial injuries not identified by CT scans.¹²

Analysis of the Relationship Test Between UCH-L1 Levels and TBI Grouping Based on GCS

Currently, brain injury biomarkers are not widely used clinically in many developed countries. The only biomarker used in clinical practice is S100B in some European countries to identify intracranial injuries in low-risk TBI patients, but it has not been recognized by the FDA and the American College of Emergency Physicians.¹²

Previous studies have shown that UCH-L1 levels significantly increase in the serum of TBI patients, including children, within the first 24 hours post-injury.^{16,18} This finding is supported by other studies on mild and moderate TBI patients due to blunt head trauma, showing serum UCH-L1 levels at 4 hours post-injury of 0.955 ± 0.248 ng/mL, higher than the negative control at 0.083 ± 0.005 ng/mL.^{23,24}

Further analysis of the diagnostic test for Rotterdam CT score and TBI grouping based on GCS showed a cut-off value of 2 with an AUC of 0.983, indicating that scores above 2 suggest moderate to severe TBI.

CONCLUSION

There is a significant relationship between serum UCH-L1 levels and the severity of TBI based on GCS, showing that severe TBI groups have higher UCH-L1 levels than moderate groups, and moderate groups have higher levels than mild groups. The Rotterdam CT score is more sensitive than serum UCH-L1 levels in predicting moderate to severe brain injuries.

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ETHICAL CONSIDERATION

The protocol of the study was approved by the Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No: 0877/KEPK/I/2024).

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CONFLICTS OF INTEREST

There is no conflict of interest in this study.

AUTHOR CONTRIBUTOR'S

All authors contributed to article preparation and paper revision and have collectively assumed responsibility for all aspects of this study.

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