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# Accuracy of D-dimer as a Predictive Biomarker for Outcome in Head Injured Patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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**A B S T R A C T**

**Introduction:** D-dimer reflects the upregulation of the overall hemostatic system upon admission. If D-dimer levels increase, coagulation disorders appear. This is considered a poor prognostic factor. High D-dimer levels reflect the severity of brain injury. Activation of systemic coagulation causes extensive intravascular fibrin deposition and a decrease in platelets and coagulation factors. This study aimed to assess the accuracy of D-dimer as a predictive biomarker for outcomes in head injury patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. **Methods:** This study is a prospective prognostic test study to test the sensitivity and specificity of D-dimer for prediction mortality in patients with severe head injuries at Dr. Mohammad Hoesin General Hospital (RSMH) Palembang in the period June 2023 to August 2023. A total of 47 research subjects participated in this study. **Results:** Post 24-hour D-dimer levels have a cut-off point of 11.78 mg/L, which has high accuracy in poor outcomes. D-dimer levels after 5 days have a cut-off point value of 2.3 mg/L and have high sensitivity in predicting poor outcomes, and the value of the difference in changes in D-dimer based on poor outcome patients have a cut-off point of 3.33 mg/L, which has a high sensitivity in predicting a poor prognosis. **Conclusion:** D-dimer levels are quite accurate as a predictive biomarker for outcomes in head injury patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

## 1. Introduction

Head injuries are one of the main causes of death and disability, with an estimated 64-74 million people per year. Traumatic head injuries are traditionally identified as mild, moderate, and severe based on the size of the Glasgow coma scale (GCS). Although most of the literature on the outcomes and long-term effects of traumatic head injuries focuses on moderate to severe cases, mild head injuries have the highest rates of emergency department visits, particularly cases of concussions and mild head injuries. Around 1.7 million people suffered head injuries, of which 52,000 died, 275,000 of whom underwent treatment in hospital. The proportion of head injuries nationally is 11.9%, with the proportion of head injuries in West Sumatra province being 14.3%, and the head injury data itself in South Sumatra has not been well recorded. Head injuries often occur in men aged 15-24 years, where the incidence of head injuries in men (55.4%) is higher than in women due to high mobility among the productive age group.[1-5]

D-dimer is a predictor for the clinical occurrence of progressive hemorrhagic injury in patients with head trauma. Time from injury to first CT,

thrombocytopenia, and plasma Fg values also show prognostic value in progressive hemorrhagic injury. The development of coagulation disorders after head injury consists of processes that lead to the conversion of fibrinogen to fibrin, an insoluble polymer which forms blood clots with trapped cellular elements. In the presence of fibrin cross-linking, D-dimer, a fibrin breakdown product in plasma, is produced by thrombin activation and the plasmin hybrid effect. When there is upregulation of fibrinolysis, D-Dimer increases upon entry in response to increased coagulation activity. Correlating with other parameters of coagulation and fibrinolysis, D-dimer reflects the upregulation of the overall hemostatic system on admission. If D-dimer levels increase, coagulation disorders appear. This is considered a poor prognostic factor. High D-dimer levels reflect the severity of brain injury. Activation of systemic coagulation causes extensive intravascular fibrin deposition and a decrease in platelets and coagulation factors.[6-10] This study aimed to assess the accuracy of D-dimer as a predictive biomarker for outcomes in head injury patients at Dr. Mohammad Hoesin Hospital, Palembang, Indonesia.

## 2. Methods

This study is a prospective prognostic test study to test the sensitivity and specificity of D-Dimer for prediction mortality in patients with severe head injuries in Dr. Mohammad Hoesin General Hospital (RSMH) Palembang in the period June 2023 to August 2023. A total of 47 research subjects participated in this study, where the research subjects met the inclusion criteria. The inclusion criteria for this study were head injury patients who came for treatment at RSMH and were willing to sign informed consent, which is filled in directly by the patient (if the patient comes fully conscious) and can be represented by the patient's legal guardian if the patient comes unconscious. This study has received approval from the medical and health research ethics committee of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

This study made observations of D-dimer levels. Results increase if the D-dimer level on day 5 is higher than the D-dimer level in the first 24 hours. Results decrease if the D-dimer level on day 5 is lower than the D-dimer level in the first 24 hours. The data obtained in this research was processed descriptively and analytically based on the number of cases obtained according to the variables studied. Variable analysis uses bivariate analysis with Chi-square tests. If the scale used is nominal, then a table with the kappa test is used. If the scale used is ordinal and interval, it must be converted to a nominal scale with an ROC cut-off value. Comparison of examination results is known by assessing correlation, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. using computer statistics SPSS (statistical package for social sciences) version 25. Significance was determined if $p < 0.05$. The research results are presented in table form which is then explained in narrative form.

## 3. Results

This study found that the average age range of patients who experienced head injuries was 20 years, the youngest age was 2 years, and the oldest age was 80 years. The age most likely to experience head injuries was 19-59 years, as many as 19 (40.4%) of the sample, and ages 13-18 years, as many as 15(31.9%). The male sample is more dominant than the female sample at 35(74.5%) samples. The mean GCS was a median of 10, with the lowest GCS being 3 and the highest being 15. The 1st D-dimer was taken 24 hours after the head injury with a mean of 7.5 mg/L, the lowest value was 0.35 mg/L, and the highest value was >20 mg/L. L, while the 2nd D-dimer was taken after 5 days from the head injury with a median of 2.1 mg/L, the lowest value was 0.05 mg/L, and the highest value was 17.89 mg/L. The mean change in D-Dimer has a median value of 3.07 mh/L, a minimum difference of -4.67 mg/L, and a maximum value of 17.87 mg/L. There were only 4 (8.5%) samples that had increased D-dimer. There were 9 (19.1%) samples who died. can be seen in Table 1.

Table 1. Characteristics of the research sample.

| Sample characteristics | n(%) | Median(min-max) |
|---|---|---|
| Age (years) | | 20(2-80) |
| 1-5 years | 3(6,4%) | |
| 6-12 years | 5(10,6%) | |
| 13-18 years | 15(31,9%) | |
| 19-59 years | 19(40,4%) | |
| ≥60 years | 5(10,6%) | |
| Gender | | |
| Male | 35(74,5%) | |
| Female | 12(25,5%) | |
| GCS | | 10(3-15) |
| 3-8 (severe head injury) | 17(36,2%) | |
| 9-13 (moderate head injury) | 18(38,3%) | |
| 14-15 (mild head injury) | 12(25,5%) | |
| 1st D-dimer (mg/L) | | 7,5(0,35- >20) |
| 2nd D-dimer (mg/L) | | 2,1(0,05-17,89) |
| D-dimer changes | | 3,07(-4,67 – 17,87) |
| Increased | 4(8,5%) | |
| Decrease | 43(91,5%) | |
| Patient outcomes | | |
| Death | 9(19,1%) | |
| Alive | 38(80,9%) | |

The D-dimer accuracy value is based on a 2x2 table analysis. This study analyzed ROC on the 1st D-dimer, 2nd D-dimer values , and the D-dimer difference. The results of the ROC analysis of the 1st D-dimer value are based on the outcome. The patient gets a value cut-off point of 11.78 with a sensitivity value of 88.9%, a specificity of 84.2%, and an AUC value of 0.915. The accuracy value of the 1st D-dimer taken ± 24 hours after the patient had a head injury can be seen in Table 2. Based on this table, the sensitivity value was 88.9%, the specificity value was 84.2%, the positive predictive value was 57.1%, and the negative predictive value was 88.9%. 96% and an accuracy value of 85.1%. From these findings, it can be concluded that the D-dimer value taken 24 hours after a head injury at 11.78 mg/L has a poor prognosis.

Table 2. Accuracy of 1st D-dimer based on patient outcome cut-off point values.

| 1st D-dimer (24 hours) | Patient outcome | | Sen | Sp | NDN | NDP | Accuracy | AUC |
|---|---|---|---|---|---|---|---|---|
| | + | - | | | | | | |
| ≥11,78 | 8 | 6 | 88,9% | 84,2% | 96% | 57,1% | 85,1% | 0,915 |
| 11,78 | 1 | 32 | | | | | | |

* outcome + = death, outcome - = alive; Sen: sensitivity; Sp: specificity; NDP: positive predictive value; NDN: negative predictive value.

The results of the ROC analysis of the 2nd D-dimer value are based on the outcome. The patient gets a value cut-off point of 2.3 with a sensitivity value of 88.9%, a specificity of 63.2%, and an AUC value of 0.807. The accuracy value of the 2nd D-dimer taken ±5 days after the patient had a head injury can be seen in Table 3. Based on this table, the sensitivity value was 88.9%, the specificity value was 63%, the positive predictive value was 36.4%, and the negative predictive value was 96%. % and an accuracy value of 68.1%. From these findings, it can be concluded that the D-dimer value taken 5 days after a head injury at 2.3 mg/L has a high sensitivity in predicting a poor prognosis.

Table 3. Accuracy of 2nd D-dimer based on patient outcome cut-off point values.

| 2nd D-dimer (5 days) | Patient outcome | | Sen | Sp | NDN | NDP | Accuracy | AUC |
|---|---|---|---|---|---|---|---|---|
| | + | - | | | | | | |
| ≥2,3 | 8 | 14 | 88,9% | 63% | 96% | 36,4% | 68,1% | 0,807 |
| <2,3 | 1 | 24 | | | | | | |

* outcome + = death, outcome - = alive; Sen: sensitivity; Sp: specificity; NDP: positive predictive value; NDN: negative predictive value.

ROC analysis results of the change value of the D-dimer difference based on the outcome the patient gets a value cut-off point of 3.33 with a sensitivity value of 88.9%, specificity of 60.5%, and an AUC value of 0.825. The accuracy value of the D-dimer difference is taken from the 24-hour D-dimer difference value minus the D-dimer value 5 days after head injury, which can be seen in Table 4. Based on this table, the sensitivity value is 88.9%, the specificity value is 60.5, the positive predictive value is 34.8%, the negative predictive value is 4.2%, and the accuracy value is 66%. From these findings, it can be concluded that a difference of 3.33 mg/L, D-Dimer from 24 hours - day 5 after head injury has a poor prognosis.

Table 4. Accuracy based on changes in D-dimer from 24 hours to 5 days.

| D-dimer changes | Patient outcome | | Sen | Sp | NDN | NDP | Accuracy | AUC |
|---|---|---|---|---|---|---|---|---|
| | + | - | | | | | | |
| ≥3,33 | 8 | 15 | 88,9% | 60,5% | 95% | 34,8% | 66% | 0,825 |
| <3,33 | 1 | 23 | | | | | | |

* outcome + = death, outcome - = alive; Sen: sensitivity; Sp: specificity; NDP: positive predictive value; NDN: negative predictive value.

**4. Discussion**

In this study, D-dimer levels taken 24 hours after a head injury at 11.78 mg/L had a poor prognosis. The 2nd D-dimer level taken on day 5 is of value cut-off point 2.3 mg/L and has high sensitivity in predicting poor prognosis. The change value of the D-dimer difference is based on the outcome. The patient gets a value cut-off point of 3.33 mg/L, which has high sensitivity in predicting poor prognosis. Another study found that the cut-off point D-dimer in brain lesions was 9 mg/L with a sensitivity of 100% and specificity of 98.5%. High levels of D-dimer are positively correlated with the duration of decreased consciousness in head injury patients with brain lesions. Another study found that a D-dimer level of 10 mg/L could predict the occurrence of intracranial injury and cranial fracture with a sensitivity of 87.8% and a specificity of 89.2%. Another study found that high D-dimer levels can predict the worsening of traumatic head injury with high sensitivity with a heterogeneity score of >90%.[11-13]

In cases of traumatic head injury in pediatric cases, another study found that the timing of the D-dimer examination could be a predictor of poor outcomes. The accuracy of D-dimer as a predictor of poor outcome is D-dimer taken 6 hours after head trauma injury has a value cut-off point ≥3.95 mg/L with a sensitivity value of 91.3% and specificity of 90%, D-dimer taken 12 hours after head trauma injury has cut off point 3.035 mg/L with a sensitivity of 91.3% and a specificity of 80% and D-dimer taken 24 hours after head injury has cut off point 1.57 with sensitivity of 87% and specificity of 70%. Another study predicted that patients with mortality 30 days after head injury experienced postoperative hypernatremia with a cut-off point of 74.1% (sensitivity = 91.9%, specificity = 56%), age has a value cut-off point of 49.5 years (sensitivity = 75.7% and specificity = 66.7%). D-dimer had a cut-off point value of 6.74 mg/L (sensitivity = 75.7% and specificity = 65.3%).[14-16]

The standard model for the coagulation system consists of two distinct physical processes:

coagulation (clot formation) and fibrinolysis (clot breakdown). Coagulation is the process by which a sequence of protein interactions ultimately leads to the formation of a fibrin clot cross-left, which physically blocks the injured area. To balance this process, fibrinolysis breaks down fibrin clots and produces fibrin degradation products, which are then removed from the system. If appropriate precautions are taken for post-head injury bleeding, this system can prevent excessive bleeding. Damage to the coagulation system causes an inability to form clots or to keep clots in place, resulting in excessive bleeding at the wound site. There are two important types of coagulation: consumptive coagulation and hyperfibrinolysis. Consumptive coagulation focuses on the inability to form fibrin clots due to the lack of necessary procoagulants, while fibrinolysis emphasizes maintaining a sufficient number of active fibrin clots due to overactive fibrinolysis. Both types of coagulation manifest as increased and uncontrolled bleeding in the wound. Other studies suggest from a clinical perspective, managing fibrinolysis is more of a concern than managing consumptive coagulopathy during the 24 hours post-treatment. Several biomarkers that can be monitored as biomarkers of bleeding and worsening in head injuries are D-dimer, fibrinogen, CRP, D-dimer /fibrinogen ratio, factor II, thrombin, and neutrophil-lymphocyte ratio. Although high D-dimer levels are associated with a poor prognosis, if the patient is given appropriate treatment, it can result in an outcome.[17-20]

## 5. Conclusion

Post-24-hour D-dimer levels have a cut-off point of 11.78 mg/L, which has high accuracy in poor outcomes. D-dimer levels after 5 days have a cut-off point value of 2.3 mg/L and have high sensitivity in predicting poor outcomes, and the value of the difference in changes in D-dimer based on poor outcome patients have a cut-off point of 3.33 mg/L, which has a high sensitivity in predicting a poor prognosis.

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