

# Patients with traumatic brain injury have fibrinolysis that is shut down and that is hyperactive

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### ABSTRACT

Coagulation/fibrinolysis diseases are linked to Traumatic Brain Injury (TBI). We looked back on 61 TBI instances that were taken to the hospital within an hour of the incident. On arrival and 3, 6, and 12 hours, 1 day, 3 days, and 7 days after injury, levels of Thrombin-Antithrombin III complex (TAT), D-dimer, and plasminogen activator inhibitor-1 (PAI-1) were assessed. The identification of predictive variables for coagulation and fibrinolysis was done using multivariate logistic regression analysis. Plasma TAT levels rose during admission and didn't start to decline until one day following the injury. Plasma D-dimer levels rose, reaching a maximum up to three hours after injury and then dropping off up to three days later.

Plasma PAI-1 levels rose up to 3 hours after injury, then continued to rise until 6 hours later, before declining until 3 days later. In cases with poor outcomes, TAT, D-dimer, and PAI-1 levels were higher during the acute period of TBI. D-dimer elevation from admission to 3 hours after injury and PAI-1 elevation from 6 hours to 1 day following injury were both significant negative prognostic markers, according to multivariate logistic regression analysis. Following a TBI, fibrinolysis, fibrinolysis shutdown, and hypercoagulation all began to occur simultaneously. Poor outcome was linked to hyperfibrinolysis immediately following injury and subsequent fibrinolysis shutdown.

**Key Words:** *Fibrinolysis; Hypercoagulation; Traumatic brain injury*

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### INTRODUCTION

Disruptions of the coagulation/fibrinolysis system have been linked to the acute phase of Traumatic Brain Injury (TBI). The mortality and functional prognosis of TBI patients are significantly impacted by the haemorrhagic diathesis linked to hyperfibrinolysis. The plasma concentration of D-dimer was found to be abnormally high in 98.7% of patients within 1 hour of injury, peaking at roughly 3 hours after injury, according to research we conducted previously on the time course of D-dimer, a marker of fibrinolysis, in patients with isolated TBI and an Abbreviated Injury Scale (AIS)7 of 3. At three months after the injury, D-dimer levels and age were independent predictors of functional prognosis. After hyperfibrinolysis, fibrinolysis is stopped by the Plasminogen Activator Inhibitor-1 (PAI-1), which is produced by vascular endothelial cells. As it relates to the use of anti-fibrinolytic drugs and thrombus development, a fuller understanding

of the aetiology of fibrinolysis shutdown is crucial. We proposed that hyperfibrinolysis and the subsequent cessation of fibrinolysis might be related to long-term prognosis. Here, concentrating on blood biomarkers, we examined the progression of coagulation anomalies, followed by fibrinolysis and fibrinolysis shutdown in the acute phase of TBI, and their association to long-term outcome.

### METHODS

#### Ethical approval and consent to participate

The 1964 Helsinki declaration and its following amendments, or equivalent ethical norms, were followed in all the study's procedures involving human subjects. Due to the study's retrospective character, the Central Ethics Committee of Nippon Medical School and the Ethics Committee of Kawaguchi Municipal Medical Center both

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authorised the study. Informed permission was also not required.

## Patients

The results of the cranial Computed Tomography (CT) were used to make the diagnosis of TBI. At the study institution, intensivists and neurointensivists separately assessed intracranial and extracranial AIS as well as CT scans. Lack of information regarding the time of the injury, the first blood draw occurring more than one hour after the injury, being younger than 16 years old, having a disease or medication that affects coagulation and fibrinolysis parameters, such as hepatic failure or anticoagulant therapy, experiencing cardiopulmonary arrest prior to admission or upon arrival, or ceasing active treatment were all exclusion criteria.

Age, sex, the Glasgow Coma Scale (GCS) score upon admission, the AIS7, the amount of Tranexamic Acid (TXA) administered, and the amount of Fresh Frozen Plasma (FFP) transfused within seven days of the injury were all gathered as case data. Acute Subdural Hematoma (ASDH), Acute Epidural Hematoma (AEDH), Intracerebral Hematoma and Contusion (ICH), and traumatic subarachnoid haemorrhage were the radiological findings that were used to categorise the type of head injury. CT scans were evaluated independently at the Time of Admission and Afterward (TSAH). Platelet count, Prothrombin Time (PT), and Activated Partial Thromboplastin Time (APTT) were evaluated throughout time, as well as the coagulation markers Thrombin-Antithrombin III complex (TAT), D-dimer, and fibrinolysis inhibition marker PAI-1.

## Management of TBI

The patients were treated in accordance with the 4th edition of the Japan Society of Neurotraumatology's Guidelines for the Management of Head Injury as soon as they arrived at the emergency room. Following thorough neurological evaluation and early stabilisation, all patients had brain CT scans. Within three hours after admission and if there were indications of deteriorating clinical symptoms or rising intracranial pressure, a second CT scan was done.

## Assessment of coagulation/fibrinolysis parameters

In Ethylenediaminetetraacetic Acid (EDTA) plasma and citrate, blood samples were taken. We used a latex immunoassay technique to measure D-dimer. Chemiluminescent enzyme immunoassay was used to quantify TAT. Using a latex immunoassay, PAI-1 was measured. A DC sheath flow detection technique was used to calculate the platelet count. By using the coagulating time method, PT was measured. A coagulating time approach was used to determine the APTT.

## Statistical analysis

Data are displayed as a percentage (%) or median. For missing data, the multiple imputation method was applied. At six months after the injury, patients were separated into two groups based on the extended Glasgow Outcome Scale (GOS-E)<sup>12,13</sup>. The GOS-E is broken down into the following eight categories: (1) dead, (2) vegetative state, (3) severe disability in lower or upper body, (4) severe disability in lower or upper body, (5) moderate disability in lower or upper body, (6) moderate disability in lower or upper body, (7) good recovery in lower or upper body. Patients with a GOS-E of 6 to 8 were in the group with a good outcome, while

those with a GOS-E of 1 to 5 were in the group with a poor prognosis. Using Student's t-test, Mann-Whitney U-test, or the 2 test for continuous normal, continuous non-normal, and dichotomous data, respectively, demographic, clinical, and radiological parameters for both groups were analysed. The plasma levels of TAT, D-dimer, and PAI-1 as well as platelet count, PT, and APTT were examined for statistically significant differences using a paired t-test at each time point. The distributions of platelet count, PT, and APTT as well as plasma levels of TAT, D-dimer, and PAI-1 were compared between the groups with favourable outcomes and those with poor outcomes at the seven measurement time points using a Generalised Linear Mixed Model (GLMM). Plasma D-dimer and PAI-1 level correlation was examined using Spearman's rank correlation coefficient.

## RESULTS

The study comprised a total of 61 consecutive TBI cases. The dataset for this investigation contained 122 missing values (5.3%) that were filled in using the multiple imputation technique. Table 1 summarises the demographic, clinical, and radiological features. 49 patients (80.3%) had ASDH, 10 patients (16.4%) had AEDH, 52 patients (85.2%) had ICH, and 58 patients (95.1%) had TSAH (some patients had more than one diagnosis). The group with a positive outcome included 30 cases (49.2%), while the group with a negative outcome included 31 cases (50.8%). Due to TBI, five patients passed away between three and seven days after an injury, while seven patients died during the first three days of an injury.

## DISCUSSION

According to this study, after a TBI, hypercoagulability, fibrinolysis, and fibrinolysis shutdown all became active one after the other, with hypercoagulability peaked right away, fibrinolysis peaked three hours later, and fibrinolysis shutdown peaked six hours later. Plasma D-dimer levels from admission to 3 h after injury and plasma PAI-1 levels from 6 h to 1 day after injury were found to be independent biomarkers of long-term outcome. It was shown that all of these coagulation and fibrinolytic changes were activated at the time of TBI in patients with poor long-term outcomes.

There are significant amounts of tissue factor in the astrocytes and cerebral arteries (TF). After a TBI, TF from the damaged brain tissue enters the bloodstream, forms a complex with factor VIIa (FVIIa), activates the extrinsic blood coagulation pathway, and increases the generation of thrombin. However, some thrombin is inactivated on endothelial cells by establishing a one-to-one complex with antithrombin III, a physiological inhibitor of thrombin. Thrombin transforms fibrinogen to fibrin and creates thrombus. This compound, known as TAT, is utilised to identify hypercoagulation in vivo by serving as a marker of thrombin generation. According to this study, hypercoagulation after TBI occurs at its height right away after injury since plasma TAT levels were abnormally high, peaking upon admission in all TBI patients and declining over time. Microthrombi have been observed to form around brain contusions as early as 1 hour after damage, according to in vivo investigations. Additionally, plasma TAT levels were higher in the group with a poor outcome than in the group with a favourable outcome, showing that hypercoagulation is connected to the development of pathology in the acute phase of TBI. A biological reaction to hypercoagulation is the activation of fibrinolysis. The fibrin breakdown product, D-dimer, is produced by plasmin, which is created following plasminogen activation by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA), in the case of fibrin clots formed by th-

-rombin involvement. Additionally, the tissue hypoperfusion brought on by trauma causes the wounded brain tissue to release a significant amount of t-PA, further triggering fibrinolysis. Thus, the hallmarks of TBI and factors in the bleeding diathesis include hyperfibrinolysis related to hypercoagulation and hyperfibrinolysis associated with direct t-PA release from the wounded brain. At the time of admission, 98.4% of the TBI patients in the current study had abnormally high plasma D-dimer levels, which peaked 3 hours after the injury. This shows that hyperfibrinolysis, which begins immediately after damage and peaks three hours later, is followed by hypercoagulation. Plasma D-dimer level from admission to 3 h after injury was an independent biomarker for long-term result, and plasma D-dimer levels were higher in the poor outcome group than in the good outcome group.

According to a report, hyperfibrinolysis during the acute phase of TBI causes hematoma expansion, which is compatible with the findings of the current investigation. The main endogenous inhibitor of fibrinolysis is PAI-1. Plasminogen is transformed into plasmin, which has proteolytic action, by the plasminogen activators t-PA and u-PA. The fibrin clot is broken down into fibrin degradation products by the key enzyme plasmin in the fibrinolytic system. Vascular endothelial cells generate and secrete PAI-1 in response to hyperfibrinolysis, direct endothelial cell injury and inflammation brought on by trauma, or tissue hypoxia brought on by thrombin generation. By blocking t-PA, u-PA, thrombomodulin, and activated protein C, it prevents fibrin clot lysis, indicating fibrinolysis shutdown. It is unclear when fibrinolysis stops after TBI, however the current study found that PAI-1 peaked 6 hours after injury and coincided with plasma D-dimer levels 3 hours later, indicating that the coagulation-fibrinolysis dynamics changed to fibrinolysis shutdown 3 hours after injury. Additionally, plasma PAI-1

levels between 6 hours and 1 day after the damage served as a separate biomarker for the long-term result. Gando demonstrated that DIC with the fibrinolytic phenotype, which progresses into DIC with the thrombotic phenotype (fibrinolysis shutdown) at a high rate and has a bad prognosis due to organ failure from thrombus formation, occurs in the acute phase of TBI.

TXA, an antifibrinolytic drug, is the sole evidence-based treatment for TBI with disruption of coagulation and fibrinolysis in a subset of patients with mild-to-moderate TBI. Adult trauma patients with significant bleeding were enrolled in the Clinical Randomisation of Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial, a sizable, international, multicenter, randomised, placebo-controlled study to determine the effect of TXA on mortality and the need for transfusion. The results revealed that all-cause mortality was significantly lower in the TXA group than in the placebo group. TXA administration decreased mortality in TBI patients compared to placebo, according to a systematic evaluation of two randomised controlled studies, including the CRASH-2 trial. However, the time of TXA treatment appears to have a significant impact on the outcomes.

### CONCLUSION

Following TBI, hypercoagulation occurred right away, fibrinolysis peaked three hours later, and fibrinolysis shutdown peaked six hours later. Patients that had poor long-term results had activation of all of these coagulation and fibrinolytic pathways. Independent indicators for long-term prognosis were plasma D-dimer levels from admission to 3 hours after injury and plasma PAI-1 levels from 6 hours to 1 day after injury.