

Original Article

Age-related differences in fibrinolytic parameters in patients with acute traumatic brain injury

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Abstract

Background: Coagulopathy and old age have been associated with poor outcomes in traumatic brain injury (TBI) patients; however, the relationships of coagulopathy and age with the acute phase of TBI remain unclear. We hypothesized that coagulation/fibrinolytic abnormalities are more severe in older patients in the acute phase of TBI and may explain, in part, their poor outcome.

Methods: We analyzed the relationship between coagulation/fibrinolytic parameters and age in the acute phase of TBI by retrospectively evaluating 274 patients with initial blood samples obtained no more than 1 hour after injury. Measurement of platelet count, prothrombin time, activated partial thromboplastin time, plasma levels of fibrinogen, and D-dimer was done in the emergency department on arrival as well as 3, 6, and 12 hours following injury. Values were compared between patients aged 16–55 years (group 1) and those aged older than 55 years (group 2) with an Abbreviated Injury Score (AIS)-head of 3–5 to identify any relationship between these parameters and age.

Results: When groups 1 and 2 were matched for AIS-head, plasma levels of D-dimer in group 2 were significantly higher than those in group 1 from hospital admission to 12 hours after injury. The Glasgow Outcome Scale scores at 3 months post-injury of group 2 with AIS 4 and 5 were significantly lower than those of group 1 (both $P < 0.0001$).

Conclusions: Fibrinolytic abnormalities are more severe in older acute-phase TBI patients, which may be a factor associated with their poor prognosis.

Key Words: Age, coagulopathy, D-dimer, fibrinolysis, traumatic brain injury

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INTRODUCTION

Increased age is associated with a poor outcome in patients with traumatic brain injury (TBI).^[1,16,20,29,30,41,42] A large-scale meta-analysis showed that old age is consistently associated with a poor outcome after TBI, with mortality and unfavorable outcomes seen in 52% and 74% of patients aged older than 55 years, respectively.^[20] TBI has been frequently associated with acute perturbations in coagulation and

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fibrinolysis.^[12,19,30,42] One recent meta-analysis found an overall prevalence of TBI-associated coagulopathy of 32.7–35.2%, and identified a marked association between abnormal hemostasis and an unfavorable outcome.^[12,19] Consistent with this, a large German trauma registry study found that 22.7% of patients with isolated TBI showed acute coagulopathy in the emergency department, which was associated with increased rates of morbidity and mortality.^[42] However, the relationship between coagulopathy and age in the acute phase of TBI remains unclear. We hypothesized that acute posttraumatic coagulation/fibrinolytic alterations are more severe in older TBI patients, and that these abnormalities comprise one of the reasons that elderly TBI patients have a poor outcome. To test this hypothesis, we evaluated the relationship between coagulation/fibrinolytic parameters and age within the first 12 hours after injury.

MATERIALS AND METHODS

Setting

The Emergency and Critical Care Center of Kawaguchi Municipal Medical Center (Saitama, Japan) is a major critical care center in Saitama Prefecture which treats approximately 1000–1200 patients per year, including 300–350 patients with severe trauma.

Patients

We retrospectively evaluated the demographic, clinical, and radiologic data of consecutive patients with TBI admitted to the center from April 2007 to June 2015. Patients with a diagnosis of severe isolated TBI were eligible, as defined previously as an intracranial Abbreviated Injury Score (AIS-head) ≥ 3 and extracranial AIS < 3 .^[12,18,26,30,38,42] Diagnosis was established based on computed tomography (CT) and magnetic resonance imaging (MRI) findings, following independent evaluation of intracranial and extracranial AIS, CT, and MRI scans by study intensivists and neurointensivists (R.N., Y.T., K.K., and Y.N.). Exclusion criteria included collection of a first blood sample more than 1 hour following injury, incomplete information concerning the time of injury, age under 16 years, infection, hematological disease, liver failure, malignancy, pregnancy, use of anticoagulant or antiplatelet agents, hypotension (SBP < 90 mmHg) or hypoxemia (PaO₂ < 60 mmHg) at the time of admission, transfusion of fresh frozen plasma (FFP) or platelets, cardiopulmonary arrest before or on arrival at hospital, death due to conditions apart than TBI, as well as incomplete information on outcome 3 months following injury. Of 405 patients with isolated TBI managed from April 2007 to June 2015, 274 patients met the inclusion criteria and were enrolled in the study. This study was approved by the hospital's Institutional Review Board.

Information on factors influencing coagulation and fibrinolytic parameters was accessed, such as

age,^[1,16,29,30,42] sex, Glasgow Coma Scale (GCS) score at admission,^[26,30,31,38,42] and AIS-head.^[1,2,26,30,42] For all patients, blood samples for the first (within 1 hour following injury) platelet count, prothrombin time (PT)-international normalized ratio (INR), activated partial thromboplastin time (aPTT), and plasma levels of fibrinogen and D-dimer were obtained on entry to the emergency department. Tests were generally repeated 3, 6, and 12 hours following injury to monitor the dynamic changes occurring in coagulation/fibrinolytic parameters in the acute phase of TBI.^[5,15,18,24,26,30,35] Admission and follow-up CT scans and MR images were evaluated independently, and head injury type was classified based on radiologic findings as acute epidural hematoma (AEDH), acute subdural hematoma (ASDH), traumatic subarachnoid hemorrhage (TSAH), and intracerebral hematoma/contusion (ICH).

Management of traumatic brain injury

Treatment was given immediately on arrival at the emergency department according to the guidelines for management of TBI developed by the Japan Society of Neurotraumatology.^[34] In all cases, patients received brain CT following detailed neurological evaluation and initial resuscitation. A second CT scan was generally obtained less than 3 hours following admission, and at any time suggested by clinical deterioration or indications of increased intracranial pressure. In cases in which CT revealed no significant abnormality but TBI was suspected, MRI was immediately obtained.

Assay of coagulation/fibrinolytic parameters

Blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) and citrate vacuum tubes. Platelet count was determined by the DC sheath flow detection method (Cellpack II® and SE sheath II®, Sysmex Corp., Kobe, Japan). PT was measured by the coagulation method (Dade Innovin®, Sysmex Corp., Kobe, Japan). APTT was quantified by the coagulation method (Thrombocheck APTT-SLA®, Sysmex Corp., Kobe, Japan). Fibrinogen was determined by the coagulation method (Thrombocheck Fib (L)®, Sysmex Corp., Kobe, Japan). D-dimer was measured by the latex immunoassay method (LIAS Auto D-dimer Neo®, Sysmex Corp., Kobe, Japan).

Statistical analysis

Data were analyzed using commercial software (SPSS Version 20.0®; IBM Corp., Armonk NY, USA). Patients were categorized by age into two groups, with Group 1 including patients aged 16–55 years and Group 2 including those aged > 55 years. This age threshold was chosen based on a report of the United States Traumatic Coma Data Bank.^[41] Glasgow Outcome Scale (GOS)^[21] scores were confirmed independently, or independently generated by study neurointensivists (R.N. and Y.T.) if unavailable by in-person contact or telephone and mail

communication with the hospital to which the patient was transferred following discharge from our hospital. For the two groups, demographic, clinical, radiologic diagnoses, and coagulation/fibrinolytic parameters were analyzed using Student's *t*-test for continuous normally distributed data, Mann-Whitney U-test for continuous non-normally distributed, or the Chi-square test for dichotomous data, with statistical significance assigned at the $P < 0.05$ level.

To evaluate the relationship of coagulation/fibrinolytic parameters to age alone, patients were divided into three groups according to AIS-head. We compared coagulation/fibrinolytic parameters between group 1 and group 2 in AIS 3 patients, AIS 4 patients, and AIS 5 patients.

RESULTS

ASDH was observed in 172 (62.8%) patients, AEDH in 46 (16.8%), ICH in 206 (75.2%), and TSAH in 226 (82.5%) (some patients had more than one diagnosis). Demographic, clinical, and radiologic diagnoses of the patients with AIS 3–5 are summarized in Tables 1–3, respectively. Overall, there were 72 AIS 3 patients (26.3%), 105 AIS 4 patients (38.3%), and 97 AIS 5 patients (35.4%). In patients with AIS 3, 4, and 5, group 1 contained significantly more males ($P = 0.030$, 0.031 , and 0.009 , respectively). The two groups did not differ by GCS score on admission. In patients with AIS 3 and 4, the radiologic diagnoses showed no significant differences between the two groups. In the patients with AIS 5, AEDH was observed in 16 (55.2%) patients in group 1 and 10 (14.7%) patients in group 2 ($P < 0.0001$). GOS scores at 3 months

post-injury in group 2 with AIS 4 and 5 were significantly lower than those of group 1 (both $P < 0.0001$).

Blood samples for coagulation and fibrinolytic parameters were collected at 0.65 ± 0.19 , 3.04 ± 0.12 , 6.05 ± 0.17 , and 12.05 ± 0.21 hours after injury for the first, second, third, and fourth sets of laboratory values, respectively. Figures 1–3 and Tables 4–6 show the time course of coagulation and fibrinolytic parameters on admission and at 3, 6, and 12 hours after injury of group 1 and group 2 matched for AIS-head. Platelet counts (normal range: $120\text{--}400 \times 10^9/\text{L}$) in group 2 were significantly lower than those in group 1 at all time points from admission to 12 hours after injury, except for the fourth platelet count in the AIS 3 and 4 patients. PT (normal range: 0.8–1.2 INR), aPTT (normal range: 24–36 seconds), and plasma fibrinogen concentration (normal range: 200–400 mg/dL) showed no significant differences between the two groups in each AIS-head of 3–5. The most marked difference between group 1 and group 2 was in the plasma level of D-dimer (normal range: 0.0–1.0 $\mu\text{g}/\text{mL}$). When groups 1 and 2 were matched for AIS-head, plasma levels of D-dimer in group 2 were significantly higher than those in group 1.

DISCUSSION

In this analysis of the time course of coagulation and fibrinolytic parameters in the acute phase of TBI, we found that coagulation parameters such as platelet count and fibrinolytic parameters such as D-dimer differed more strongly between groups 1 and 2 than coagulation parameters such as PT, aPTT, and fibrinogen. In particular, D-dimer showed age-related differences at all time points in each AIS-head of 3 to 5 from admission to 12 hours after injury.

Table 1: Demographic, clinical, and radiologic diagnoses of patients with AIS-head 3

	Total (n=72)	Group 1 (n=47)	Group 2 (n=25)	P
Demographic data				
Age (median; 25 th –75 th percentiles)	47 (30-63)	36 (23-46)	70 (63-82)	<0.0001
Male (n; %)	54 (75.0)	38 (80.9)	16 (64.0)	0.030
GCS scores on admission				
15-13 (n; %)	48 (66.6)	32 (68.1)	16 (64.0)	0.42
12-9 (n; %)	12 (16.7)	6 (12.8)	6 (24.0)	
8-3 (n; %)	12 (16.7)	9 (19.1)	3 (12.0)	
Radiologic diagnosis				
ASDH (n; %)	0 (0)	0 (0)	0 (0)	
AEDH (n; %)	0 (0)	0 (0)	0 (0)	
ICH (n; %)	41 (56.9)	28 (59.6)	13 (52.0)	0.54
TSAH (n; %)	58 (80.6)	36 (76.6)	22 (88.0)	0.23
GOS scores at 3 months post-injury				
5-4 (n; %)	68 (94.4)	46 (97.9)	22 (88.0)	0.09
3-1 (n; %)	4 (5.6)	1 (2.1)	3 (12.0)	

AIS: Abbreviated Injury Score, Group 1: Patients aged 16-55 years, Group 2: Patients aged older than 55 years, GCS: Glasgow Coma Scale, ASDH: Acute subdural hematoma, AEDH: Acute epidural hematoma, ICH: Intracerebral hematoma/contusion, TSAH: Traumatic subarachnoid hemorrhage, GOS: Glasgow Outcome Scale, GOS score of 1 indicates death, 2: Persistent vegetative state, 3: Severe disability, 4: Moderate disability, and 5: Good recovery

Several studies have demonstrated that platelet count decreases with age.^[3,33,40] A large sample size cohort study showed that platelet counts in the age range 15–64 years were significantly higher than in participants >64 years (252 vs. 233 × 10⁹/L, *P* < 0.001).^[3] Segal *et al.* also demonstrated that the platelet count

remains relatively stable during middle age (25–60 years) but falls in older age (>60), decreasing by approximately 8%, or 20 × 10⁹/L, between 50- to 59-year-old participants and those >70 years of age.^[33] Concerning the mechanisms of these age-related changes, this may reflect a reduction in hematopoietic stem cell reserve with aging or a survival advantage in subjects with lower (but still within the normal range) platelet counts.^[3] Because almost all platelet counts in the present study were within the normal range, this suggests that the platelet counts in group 2 were lower than in group 1 due not only to TBI but also to aging factors.

Table 2: Demographic, clinical, and radiologic diagnoses of patients with AIS-head 4

	Total (n=105)	Group 1 (n=45)	Group 2 (n=60)	P
Demographic data				
Age (median; 25 th -75 th percentiles)	61 (40-71)	35 (24-47)	68 (63-78)	<0.0001
Male (n; %)	75 (71.4)	37 (82.2)	38 (63.3)	0.031
GCS scores on admission				
15-13 (n; %)	61 (58.1)	27 (60.0)	34 (56.7)	0.61
12-9 (n; %)	16 (15.2)	8 (17.8)	8 (13.3)	
8-3 (n; %)	28 (26.7)	10 (22.2)	18 (30.0)	
Radiologic diagnosis				
ASDH (n; %)	87 (82.9)	35 (77.8)	52 (86.7)	0.23
AEDH (n; %)	20 (19.0)	12 (26.7)	8 (13.3)	0.087
ICH (n; %)	80 (76.2)	32 (71.1)	48 (80.0)	0.29
TSAH (n; %)	83 (79.0)	34 (75.6)	49 (81.7)	0.45
GOS scores at 3 months post-injury				
5-4 (n; %)	85 (81.0)	45 (100)	40 (66.7)	<0.0001
3-1 (n; %)	20 (19.0)	0 (0)	20 (33.3)	

AIS: Abbreviated Injury Score, Group 1: Patients aged 16-55 years, Group 2: Patients aged older than 55 years, GCS: Glasgow Coma Scale, ASDH: Acute subdural hematoma, AEDH: Acute epidural hematoma, ICH: Intracerebral hematoma/contusion, TSAH: Traumatic subarachnoid hemorrhage, GOS: Glasgow Outcome Scale, GOS score of 1 indicates death, 2: Persistent vegetative state, 3: severe disability, 4: Moderate disability, and 5: Good recovery

The early hypercoagulable state after TBI is followed by an increase in fibrinolytic activity, with fibrinolytic parameters such as fibrin/fibrinogen degradation products (FDP) and D-dimer being reliable prognostic markers.^[9,22,30,31,37] Hyperfibrinolysis can cause hemorrhage extension by degradation of coagulation factors, breakdown of formed fibrin clot, and impaired clot formation due to excess generation of fibrin degradation products, and hemorrhagic lesions due to hypocoagulability are a critical and often fatal complication of TBI.^[1,19,30,36] Recently, several articles have described the time course of coagulation/fibrinolytic parameters in the acute phase of TBI.^[5,15,18,24,26,30,35] We showed that fibrinolytic parameters such as D-dimer differed more strongly between the good outcome and poor outcome patients than differences in coagulation parameters such as platelet count, PT, aPTT, and fibrinogen through the acute phase of TBI. We also concluded that D-dimer was the most accurate coagulation/fibrinolytic factor predicting outcome.^[30]

We observed that the median plasma level of D-dimer was higher in group 2 than in group 1 in AIS-head

Table 3: Demographic, clinical, and radiologic diagnoses of patients with AIS-head 5

	Total (n=97)	Group 1 (n=29)	Group 2 (n=68)	P
Demographic data				
Age (median; 25 th -75 th percentiles)	65 (51-72)	37 (31-48)	70 (65-76)	<0.0001
Male (n; %)	66 (68.0)	25 (86.2)	41 (60.3)	0.009
GCS scores on admission				
15-13 (n; %)	19 (19.6)	7 (24.1)	12 (17.7)	0.25
12-9 (n; %)	16 (16.5)	7 (24.1)	9 (13.2)	
8-3 (n; %)	62 (63.9)	15 (51.8)	47 (69.1)	
Radiologic diagnosis				
ASDH (n; %)	85 (87.6)	24 (82.8)	61 (89.7)	0.35
AEDH (n; %)	26 (26.8)	16 (55.2)	10 (14.7)	<0.0001
ICH (n; %)	85 (87.6)	24 (82.8)	61 (89.7)	0.35
TSAH (n; %)	85 (87.6)	25 (86.2)	60 (88.2)	0.78
GOS scores at 3 months post-injury				
5-4 (n; %)	39 (40.2)	21 (72.4)	18 (26.5)	<0.0001
3-1 (n; %)	58 (59.8)	8 (27.6)	50 (73.5)	

AIS: Abbreviated Injury Score, Group 1: Patients aged 16-55 years, Group 2: Patients aged older than 55 years, GCS: Glasgow Coma Scale, ASDH: Acute subdural hematoma, AEDH: acute epidural hematoma, ICH: Intracerebral hematoma/contusion, TSAH: Traumatic subarachnoid hemorrhage, GOS: Glasgow Outcome Scale, GOS score of 1 indicates death, 2: Persistent vegetative state, 3: Severe disability, 4: Moderate disability, and 5: Good recovery

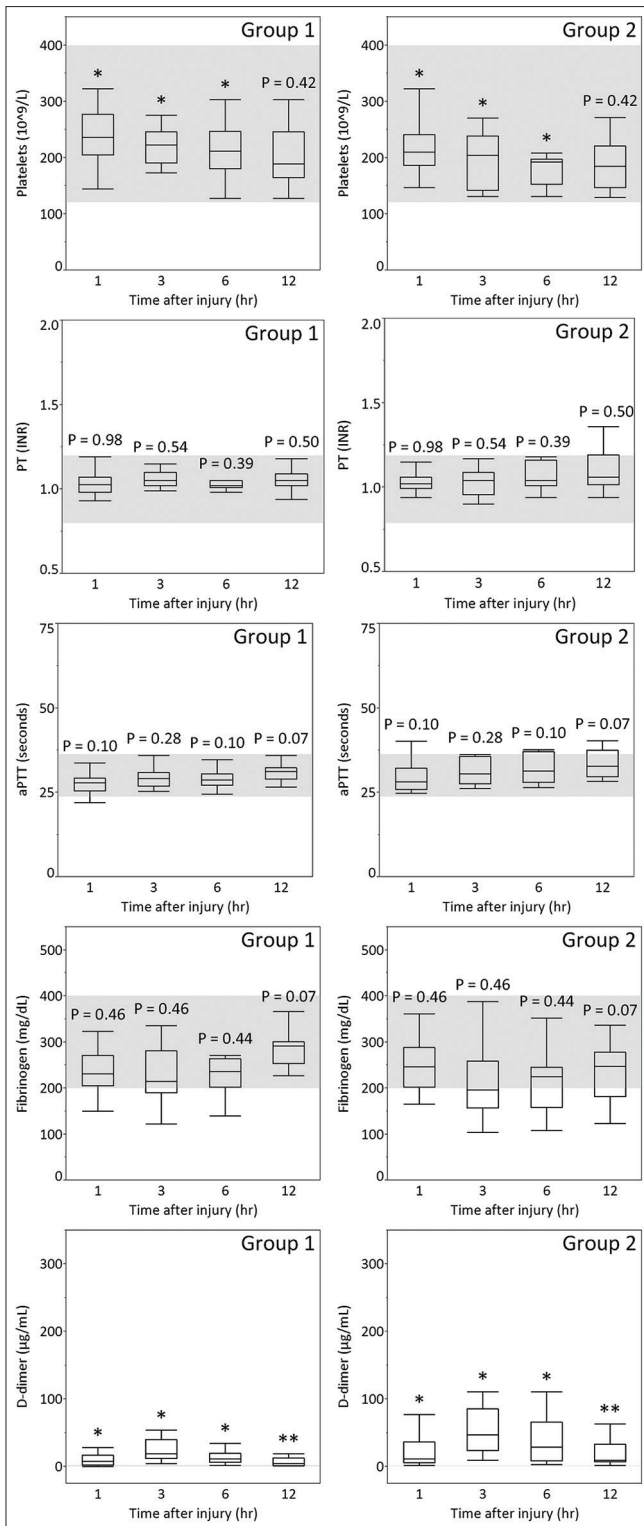


Figure 1: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or aged older than 55 years (Group 2) with AIS-head 3 on admission and at 3, 6, and 12 hours after TBI. The gray zones represent the normal ranges for each parameter. *P < 0.05, **P < 0.01

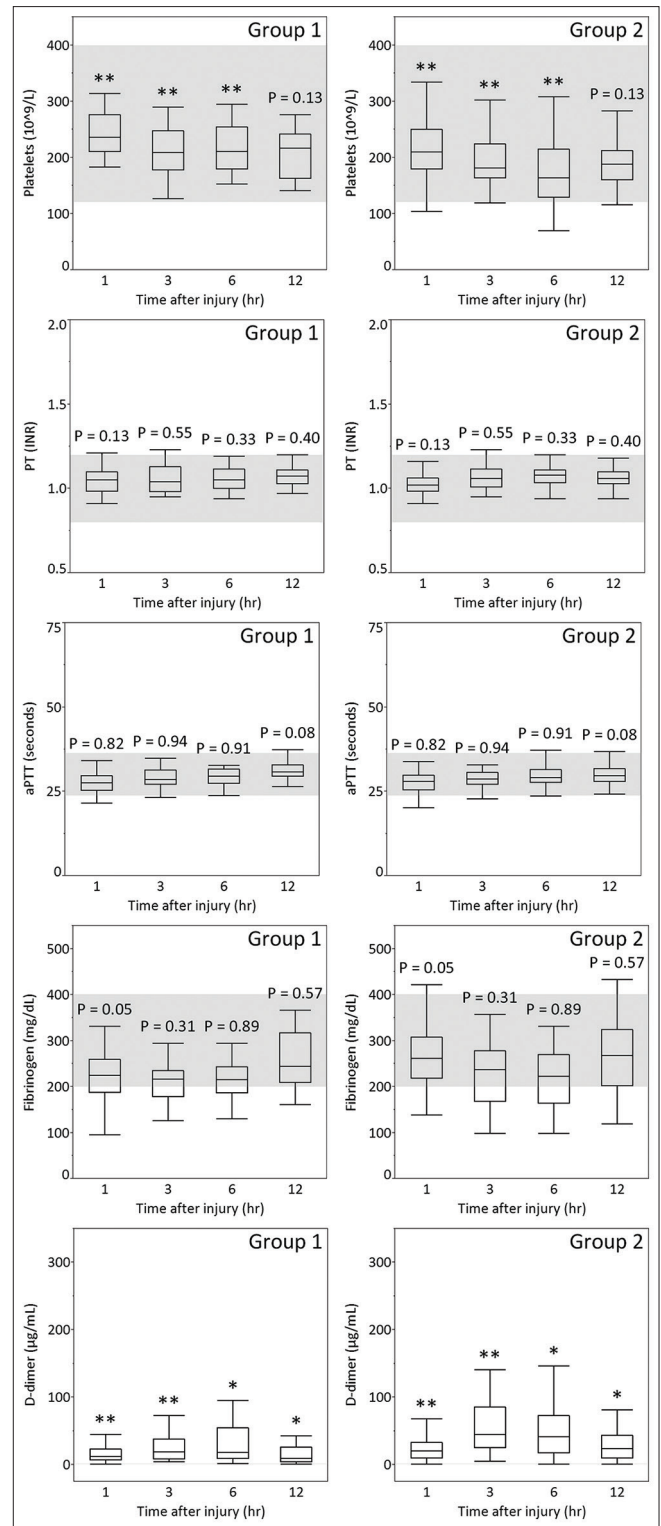


Figure 2: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or aged older than 55 years (Group 2) with AIS-head 4 on admission and at 3, 6, and 12 hours after TBI. The gray zones represent the normal ranges for each parameter. *P < 0.05, **P < 0.01

matched patients from admission to 12 hours after injury [Figures 1–3; Tables 4–6]. Several reports have shown that older individuals have increased baseline

D-dimer levels.^[4,10,13,14,17,23,27,28,32,39] In older-aged patients, an increasing number of healthy individuals have heightened coagulation enzyme activity, accompanied

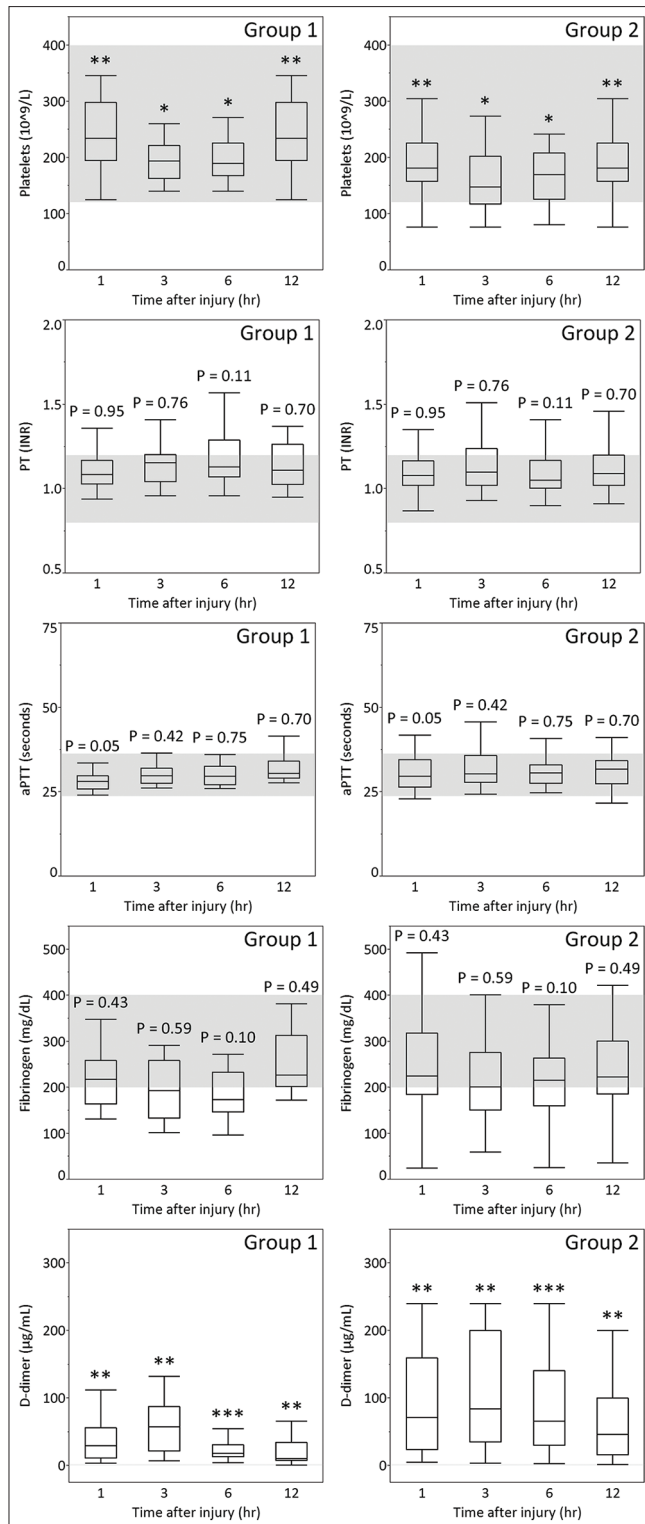


Figure 3: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16–55 years (Group 1) or aged older than 55 years (Group 2) with AIS-head 5 on admission and at 3, 6, and 12 hours after TBI. The gray zones represent the normal ranges for each parameter. * $P < 0.05$, ** $P < 0.01$, * $P < 0.001$**

by signs of enhanced formation of fibrin and secondary hyperfibrinolysis.^[27,28] Pieper demonstrated that one of the reasons for higher D-dimer levels in the elderly is

enhanced production of tissue factor in response to a given level of cytokine stimulus from endothelial cells.^[32] Lee *et al.* also demonstrated that age-related changes in D-dimer concentrations may be the reason for the increase in the turnover of fibrin and may be associated with the age-related increases in endothelial disturbance and the prevalence of atherosclerosis.^[25] However, the relationship between elevation of plasma D-dimer and age after TBI remains unclear. We detected the onset of hyperfibrinolysis within the first hour after injury, which is signaled by high plasma levels of D-dimer. Yokota *et al.* showed that poor outcomes after TBI in elderly patients were associated with activation of the cerebral endothelium, as measured by the increased serum levels of thrombomodulin and von Willebrand factor, compared to young and middle-aged patients.^[43] In another study, they also showed that the levels of von Willebrand factor paralleled plasma FDP levels.^[44] These results support the hypothesis that fibrinolytic abnormalities increase in older TBI patients because of the high sensitivity of cerebral endothelial cells to trauma.

D-dimer as a fibrinolytic parameter progressively increased from admission to 3 hours after injury and remained raised for at least a further 12 hours, indicating that presentation within 12 hours after injury carries a high risk of exacerbation of hemorrhage due to hyperfibrinolysis, especially within 3 hours after injury. Allard *et al.* reported that mortality increased four-fold (32% vs. 8%) on follow-up CT scan in coagulopathic patients with hemorrhagic progression.^[1] The most important risk factor for progression of hemorrhagic lesions was coagulopathy occurring in the first 24 hours after TBI.^[1] We consider that hyperfibrinolysis can cause hemorrhage expansion via the degradation of coagulation factors, breakdown of the formed fibrin clot, and impairment of clot formation as a result of excessive generation of fibrin degradation products. We consider that fibrinolytic abnormalities, which are represented by elevation in the plasma level of D-dimer, increase more steeply in older patients in the acute phase of TBI, and that fibrinolytic abnormalities are one of the factors involved in the poorer outcome that older TBI patients experience. Further investigation of the physiological and pathophysiological features in the aging brain may aid development of preventive solutions.

Our results suggest that the correction of coagulopathy caused by hyperfibrinolysis may be especially important in the treatment of geriatric TBI. The Clinical Randomisation of Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial is a major international multicenter randomized placebo-controlled study of the impact of the antifibrinolytic agent tranexamic acid (TXA) on death and requirements for transfusion in adult trauma patients suffering significant hemorrhage.^[8] This study provided additional insight into the treatment of trauma patients with antifibrinolytic agents but was

Table 4: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16-55 years (group 1) and aged >55 years (group 2) with AIS-head 3, on admission and at 3, 6, and 12 hours after traumatic brain injury

Factor	Admission			3 hours after injury			6 hours after injury			12 hours after injury		
	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P
Platelets ($10 \times 10^9/L$)	236 (205-277)	210 (186-241)	0.028	223 (190-246)	204 (142-239)	0.037	212 (180-247)	192 (153-197)	0.042	189 (165-246)	185 (147-221)	0.42
PT (INR)	1.03 (0.98-1.07)	1.02 (0.99-1.06)	0.98	1.05 (1.02-1.10)	1.04 (0.96-1.09)	0.54	1.02 (1.01-1.05)	1.04 (1.01-1.16)	0.39	1.05 (1.02-1.09)	1.06 (1.02-1.19)	0.50
aPTT (seconds)	27.9 (25.4-29.2)	28.1 (25.6-32.2)	0.10	29.1 (26.9-30.9)	30.5 (27.5-35.7)	0.28	28.7 (27.2-30.5)	31.3 (28.0-37.1)	0.10	31.3 (29.0-32.4)	32.8 (29.7-37.6)	0.07
Fibrinogen (mg/dL)	231 (205-271)	246 (202-289)	0.46	214 (190-281)	197 (157-259)	0.46	237 (202-264)	225 (158-245)	0.44	292 (253-300)	248 (181-278)	0.07
D-dimer ($\mu g/mL$)	7.7 (2.6-16.8)	11.6 (5.7-36.8)	0.029	19.2 (11.9-40.2)	47.2 (24.1-85.9)	0.041	11.3 (6.4-19.6)	28.7 (8.7-66.0)	0.045	4.1 (1.7-12.5)	9.3 (7.0-33.1)	<0.01

Values are the median (25th-75th percentiles), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, AIS: Abbreviated Injury Score, INR: International normalized ratio

Table 5: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16-55 years (group 1) and aged >55 years (group 2) with AIS-head 4, on admission and at 3, 6, and 12 hours after traumatic brain injury

Factor	Admission			3 hours after injury			6 hours after injury			12 hours after injury		
	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P
Platelets ($10 \times 10^9/L$)	236 (211-277)	210 (180-250)	<0.01	209 (178-248)	181 (164-225)	<0.01	211 (180-254)	164 (129-215)	<0.01	217 (163-242)	188 (160-212)	0.13
PT (INR)	1.05 (0.99-1.10)	1.02 (0.99-1.06)	0.13	1.04 (0.98-1.13)	1.06 (1.01-1.12)	0.55	1.05 (1.00-1.12)	1.08 (1.04-1.11)	0.33	1.08 (1.03-1.11)	1.06 (1.03-1.10)	0.40
aPTT (seconds)	27.6 (25.4-29.6)	28.0 (25.5-29.9)	0.82	28.6 (27.1-31.3)	28.7 (27.2-30.7)	0.94	29.5 (27.4-31.6)	29.1 (27.7-31.6)	0.91	30.8 (29.5-32.9)	29.7 (28.0-31.7)	0.08
Fibrinogen (mg/dL)	225 (188-260)	262 (219-308)	0.05	216 (179-235)	237 (168-278)	0.31	215 (187-243)	223 (164-270)	0.89	245 (209-317)	268 (202-324)	0.57
D-dimer ($\mu g/mL$)	12.3 (6.9-23.3)	20.2 (10.2-33.3)	<0.01	18.9 (8.7-37.8)	45.3 (25.2-85.3)	<0.01	18.3 (9.3-54.7)	41.5 (17.7-73.0)	0.032	9.2 (4.6-26.0)	24.2 (10.1-43.7)	0.011

Values are the median (25th-75th percentiles), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, AIS: Abbreviated Injury Score, INR: International normalized ratio

Table 6: Platelet count, PT, aPTT, and plasma levels of fibrinogen and D-dimer of patients aged 16-55 years (group 1) and aged >55 years (group 2) with AIS-head 5, on admission and at 3, 6, and 12 hours after traumatic brain injury

Factor	Admission			3 hours after injury			6 hours after injury			12 hours after injury		
	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P	Group 1	Group 2	P
Platelets ($10 \times 10^9/L$)	234 (195-298)	182 (158-226)	<0.01	194 (163-222)	148 (118-203)	0.045	190 (168-226)	170 (126-209)	0.032	234 (195-298)	182 (158-226)	<0.01
PT (INR)	1.09 (1.03-1.17)	1.08 (1.02-1.17)	0.95	1.16 (1.04-1.20)	1.10 (1.02-1.24)	0.76	1.13 (1.07-1.29)	1.05 (1.01-1.17)	0.11	1.11 (1.03-1.27)	1.09 (1.02-1.20)	0.70
aPTT (seconds)	28.1 (26.0-29.8)	29.6 (26.5-34.5)	0.05	29.8 (27.6-32.1)	30.4 (27.9-35.9)	0.42	29.6 (27.2-32.6)	30.7 (27.5-33.0)	0.75	30.5 (29.1-34.2)	31.8 (27.5-34.4)	0.70
Fibrinogen (mg/dL)	218 (164-259)	225 (185-318)	0.43	193 (133-259)	201 (151-276)	0.59	173 (147-233)	215 (161-264)	0.10	227 (202-313)	223 (186-301)	0.49
D-dimer ($\mu g/mL$)	29.8 (11.3-55.8)	71.4 (23.9-159.7)	<0.01	57.5 (22.2-87.6)	83.8 (35.2-200.0)	<0.01	18.3 (13.8-31.0)	66.1 (30.1-141.1)	<0.001	10.6 (7.8-34.4)	46.5 (16.4-100.3)	<0.01

Values are the median (25th-75th percentiles). PT: Prothrombin time, aPTT: Activated partial thromboplastin time, AIS: Abbreviated Injury Score, INR: International normalized ratio

unable to confirm whether the progression of lesions was decreased or outcomes were improved following TBI.^[7] Future research should prioritize evaluation of the benefit of early treatment of coagulation disorders in TBI in well-performed blinded randomized trials; in particular, we look forward to the results of the ongoing CRASH-3 and Resuscitation Outcome Consortium (ROC) TXA trials.^[6,11]

Limitations

Several limitations of our study warrant mention. First, the study was not designed to investigate the effect of surgery or hemodilution due to osmotic diuretic agents, which might affect coagulation or fibrinolytic variables at 3, 6 and 12 hours post-injury. Second, differences in the mechanism of TBI between Japan and other countries are probably due to the high mean age of Japanese, which would result in an apparent overrepresentation of older patients with severe TBI. Calculation of the GOS score at 3 months may be somewhat early with severe TBI. Evaluating of recovery after severe TBI needs ongoing investigation and implementation of long-term follow-up.

CONCLUSIONS

Fibrinolytic abnormalities are more severe in older TBI patients in the acute phase, and appear to be one of the reasons why older TBI patients have a poor outcome. Future studies should reveal whether early recognition of acute coagulopathy and the prevention of delayed hemostatic disturbances might be associated with improvements in morbidity and mortality in older TBI patients.

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Conflicts of interest

There are no conflicts of interest.

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