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RESEARCH

The time course of alpha 2-plasmin inhibitor and plasmin-alpha 2-plasmin inhibitor complex levels in patients with traumatic brain injury

Takahiro Kanaya[1] · Ryuta Nakae[1] · Tetsuro Sekine[2] · Yu Fujiki[3] · Yasuhiro Takayama[1] · Yutaka Igarashi[1] · Go Suzuki[3] · Yasutaka Naoe[3] · Hiroyuki Yokota[4] · Shoji Yokobori[1]

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Abstract

Background In its acute phase, traumatic brain injury (TBI) is notable for disturbances in the coagulation/fibrinolysis system. Plasmin, alpha 2-plasmin inhibitor (α2-PI), and their complex (plasmin-α2-PI complex [PIC]) are important components of the coagulation-fibrinolytic system, but their time courses in the acute phase of TBI and their association with long-term prognosis are unknown.

Methods We conducted a retrospective analysis of 84 consecutive patients with isolated TBI, during which plasma α2-PI and PIC levels were measured at the time of arrival, as well as at 3, 6, and 12 h, and on days 1, 3, and 7 post-injury. Differences in plasma α2-PI and PIC levels between the good outcome group (extended Glasgow Outcome Scale [GOS-E] of 5–8 at 6 months post-injury) and the poor outcome group (GOS-E of 1–4 at 6 months post-injury) were analyzed using a generalized linear mixed model (GLMM). The hematoma volume of the initial CT scan upon admission and the follow-up CT scan was evaluated using CT volumetry, and then the relationship between changes in hematoma volume and plasma levels of α2-PI and PIC at admission was examined.

Results Abnormally high plasma PIC levels were observed at admission in 97.6% of the patients. In the GLMM adjusted for covariates, the poor outcome group had significantly lower plasma α2-PI activity from admission to 3 days post-injury and significantly higher plasma PIC levels from admission to 6 h post-injury compared to the good outcome group. A negative correlation was found between α2-PI activity at admission and changes in hematoma volume (Spearman's correlation coefficient, $r = -0.587$, $p = 0.001$).

Conclusions These findings suggest that plasmin was activated and fibrinolysis enhanced immediately after injury in most patients, while in a subset of patients, hematoma expansion due to the suppression of fibrinolytic inhibition by α2-PI negatively affected the outcome.

Keywords Traumatic brain injury · Blood coagulation disorders · Fibrinolysis · Alpha-2-antiplasmin · Prognosis

✉ Ryuta Nakae
nakae@nms.ac.jp

[1] Department of Emergency and Critical Care Medicine, Nippon Medical School Hospital, 1-1-5, Sendagi, Bunkyo-Ku, Tokyo 113-8603, Japan

[2] Department of Radiology, Nippon Medical School Musashi Kosugi Hospital, Kawasaki, Kanagawa, Japan

[3] Emergency and Critical Care Center, Kawaguchi Municipal Medical Center, Kawaguchi, Saitama, Japan

[4] Graduate School of Medical and Health Science, Nippon Sport Science University, Yokohama, Kanagawa, Japan

Abbreviations

AEDH	Acute epidural hematoma
AIS	Abbreviated injury scale
ASDH	Acute subdural hematoma
CT	Computed tomography
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
GLMM	Generalized linear mixed model
GOS-E	Extended Glasgow Outcome Scale
ICH	Intracerebral hematoma and contusion
IQR	Interquartile range
PIC	Plasmin-alpha 2-plasmin inhibitor complex
TBI	Traumatic brain injury
TSAH	Traumatic subarachnoid hemorrhage

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TXA	Tranexamic acid
t-PA	Tissue-type plasminogen activator
u-PA	Urokinase-type plasminogen activator
α2-PI	Alpha 2-plasmin inhibitor

Introduction

The acute phase of traumatic brain injury (TBI) involves disturbances of the coagulation-fibrinolytic system [7, 10, 26, 35], characterized by hypercoagulability immediately after injury and subsequent enhanced fibrinolytic activity [27]. In particular, hyperfibrinolysis is closely related to outcome because it induces a hemorrhagic diathesis and is associated with hematoma expansion [1, 17, 26, 27, 32].

Plasmin plays an important role in the fibrinolytic system. Fibrin clots formed as a result of blood coagulation are degraded by plasmin generated from the activation of plasminogen by tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) (secondary fibrinolysis) [8]. In severe trauma, pathological degradation of fibrinogen by plasmin occurs separately from coagulation activation and thrombus formation (primary fibrino[geno] lysis) [19, 34]. Alpha 2-plasmin inhibitor (α2-PI) is a fibrinolysis inhibitor that forms a one-to-one complex with plasmin (plasmin-α2-PI complex [PIC]) and inactivates its enzymatic activity. Familiarity with α2-PI and PIC is important in the study of coagulation and fibrinolysis, but their time course in the acute phase of TBI and their effect on long-term prognosis are unknown. We sought to examine the relationship between the time courses of α2-PI and PIC levels in the acute phase of TBI and their relationship to long-term prognosis.

Materials and methods

Ethical considerations

The Central Ethics Committee of Nippon Medical School (Approval #M-2021–025, dated 16 February 2022) and the Ethics Committee of Kawaguchi Municipal Medical Center (Approval #2021–35, dated 7 March 2022) approved this study. Data were anonymized. Individual written consent was waived due to the retrospective nature of the study.

Patient population

The demographic, clinical, and imaging data of TBI patients admitted to Kawaguchi Municipal Medical Center from April 2018 to June 2023 were analyzed. We included cases with an isolated diagnosis of TBI with an intracranial Abbreviated Injury Scale (AIS) [2] score ≥ 3 and an extracranial AIS < 3, as described previously [7, 26, 27, 35].

A TBI diagnosis was made from head computed tomography (CT) findings. Intracranial and extracranial AIS and CT scans were evaluated independently by intensivists and neurointensivists (T.K., Y.F., G.S., Y.N.) at the Department of Emergency and Critical Care Medicine, Nippon Medical School, Tokyo, and the Emergency and Critical Care Center, Kawaguchi Municipal Medical Center, Saitama, both in Japan.

Cases were excluded if there was incomplete information about the time of injury, if the first blood draw was > 1 h after injury, age was < 16 y, if there were diseases that affect coagulation and fibrinolysis parameters such as hepatic failure, if the patients were being treated with anticoagulant medication, if cardiopulmonary arrest had occurred prior to admission or on arrival, and withdrawal from active treatment in compliance with the patient's own advance care planning or the family's decision.

Data on age, sex, admission Glasgow Coma Scale (GCS) score, AIS, administration of tranexamic acid (TXA), volume of fresh frozen plasma (FFP) transfused within 7 days of injury, and whether surgery for TBI was performed were collected. Admission head CT scans and all subsequent head CT scans were evaluated independently, with classification of the type of head injury identified on CT as acute subdural hematoma (ASDH), acute epidural hematoma (AEDH), traumatic subarachnoid hemorrhage (TSAH), and intracerebral hematoma and contusion (ICH), or a combination of two or more. We evaluated the plasma levels of α2-PI and PIC at seven predetermined time points: upon arrival at the emergency department (within 1 h of injury) and at 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after injury.

Management

Upon arrival, patients were treated following the Guidelines for the Management of Head Injury, 4th edition, of the Japan Society of Neurotraumatology [9]. After detailed neurological evaluation and initial stabilization, all patients underwent a head CT. A second scan was performed within 3 h of admission, or if worsening clinical symptoms or increased intracranial pressure were observed.

Coagulation/fibrinolysis parameter assessment

Blood samples were drawn into citrate. α2-PI was measured using a synthetic chromogenic substrate method (Testzym S APL®, Sekisui Medical Corp., Tokyo, Japan). PIC was measured using a latex photometric immunoassay method (LPIA-ACE PPI II®, LSI Medience Corp., Tokyo, Japan).

Evaluation of traumatic intracranial hematoma volume

We evaluated the hematoma volume of the initial CT scan upon admission and the follow-up CT scan using CT volumetry, with the patient undergoing follow-up observation with CT scans without surgery (Fig. 1). Hematoma quantification was performed using the VINCENT brain analysis package Version 7.2® (Fujifilm, Tokyo, Japan) software with semi-automatic analysis. This software employs an analytical model that integrates rule-based processing with deep learning, utilizing 3D-Unet for the deep learning component. The algorithm applies the following criteria: regions with signal intensities relatively higher than those of the surrounding brain tissue are considered positive, regions with signal intensities equal to or exceeding those of the skull are considered negative, and images showing significant quality degradation due to artifacts or displaying anatomical deviations caused by surgical intervention or TBI are excluded. Based on these criteria, multiple regions suspected to represent hematoma are extracted, after which the user confirms the acceptability of each region. This analysis was performed by a neuroradiologist (T.S.) with over 15 years of clinical experience, who was unaware of the patient's background or clinical information, and each case was processed in approximately 5 min. We then examined the relationship between changes in hematoma volume and plasma levels of α2-PI and PIC at the time of admission.

Statistical analysis

Data are expressed as either number (percentage) or median (interquartile range [IQR]). Missing data were addressed using the multiple imputation method [14, 21]. The extended

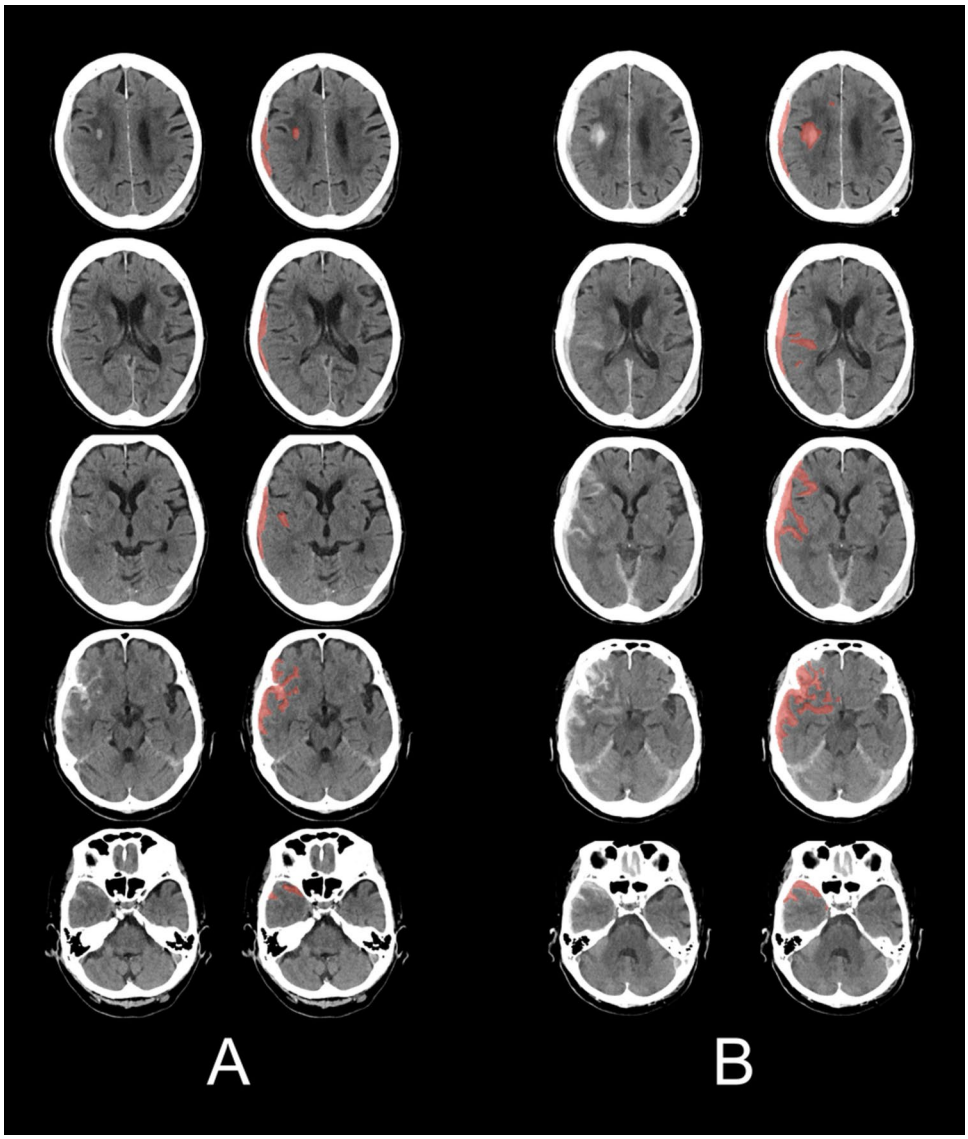

Fig. 1 A head CT scan of a 79-year-old female with traumatic brain injury. The left two columns show the initial CT scan upon admission (**A**), while the right two columns display the follow-up CT scan taken 120 min later (**B**). On each side, the left shows the original CT scan, and the right shows the CT scan with the hematoma highlighted in red. Acute subdural hematoma, cerebral contusion, and traumatic subarachnoid hemorrhage were observed, with successful segmentation of the hematoma regions based on attenuation values above a certain threshold. No misclassification of bone or calcification was observed. In this case, the hematoma volume on the initial CT scan was 30.1 mL, while the hematoma volume on the follow-up CT scan was 59.6 mL

Glasgow Outcome Scale (GOS-E) [15, 36] was used to categorize outcomes as follows: (1) dead, (2) vegetative state, (3) lower body severe disability, (4) upper body severe disability, (5) lower body moderate disability, (6) upper body moderate disability, (7) lower body good recovery, and (8) upper body good recovery. The cases were classified into two groups: the good outcome group (GOS-E of 5–8 at 6 months post-injury) and the poor outcome group (GOS-E of 1–4 at 6 months post-injury). Neurointensivists (T.K. and Y.F.) at the study institution evaluated the GOS-E. Follow-up information was collected through telephone and mail communications with patients, their families, and the hospitals they were transferred to after discharge. Demographic, clinical, and imaging data were analyzed using Student's *t*-test for normally distributed continuous variables, the Mann–Whitney *U*-test for non-normally distributed continuous variables, and the $\chi 2$ test for categorical variables. Paired *t*-tests were employed to assess for statistically significant differences in plasma α2-PI and PIC levels at various time points. Plasma α2-PI and PIC level distributions between the good and poor outcome groups across seven time points were analyzed using a generalized linear mixed model (GLMM) with covariates adjusted. Multiple logistic regression analysis was conducted to identify independent risk factors at admission associated with poor prognosis. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SPSS Version 27.0® (IBM Corp., Armonk, NY, USA).

Results

Patients

The study included 84 consecutive cases of TBI. There were 81 missing values (3.9%) in this study's dataset, which were provided by the multiple imputation method. Table 1 provides a summary of the clinical, demographic, and imaging characteristics. ASDH was present in 70 patients (83.3%), AEDH in 18 patients (21.4%), ICH in 72 patients (85.7%), and TSAH in 77 patients (91.7%), with some patients having multiple diagnoses. The good outcome group comprised 41 cases (48.8%), while the poor outcome group included 43 cases (51.2%). Among the patients, 9 died between 1 and 3 days post-injury, and 5 died between 3 and 7 days post-injury due to TBI. The median age was significantly lower in the good outcome group than in the poor outcome group (median 53 years [IQR 34–68 years] vs. 78 years [IQR 59–83 years], $p < 0.001$). No significant differences were observed in gender distribution between the groups. The good outcome group demonstrated higher GCS scores at admission (median 13 [IQR 9–15] vs. 6 [IQR 4–11], $p < 0.001$), lower AIS-head scores (median 4 [IQR 3–5] vs. 5 [IQR 5–5], $p < 0.001$), a lower incidence of ASDH (70.7% vs. 95.3%, $p = 0.002$), reduced FFP transfusion volumes (median 0 mL [IQR 0–280 mL] vs. 720 mL [IQR 0–1200 mL], $p = 0.01$), and a lower rate of surgical intervention (29.3%

Table 1 Initial clinical, demographic, and imaging characteristics of the study population

	Total ($n = 84$)	Good outcome group ($n = 41$)	Poor outcome group ($n = 43$)	*p*
Demographic data				
Age, median (IQR), y	66 (42–80)	53 (34–68)	78 (59–83)	< 0.001
Male, *n* (%)	54 (64.3)	28 (68.3)	26 (60.5)	0.45
Clinical scores				
GCS score, median (IQR)	10 (6–14)	13 (9–15)	6 (4–11)	< 0.001
AIS-head, median (IQR)	5 (4–5)	4 (3–5)	5 (5–5)	< 0.001
Head CT findings				
ASDH, *n* (%)	70 (83.3)	29 (70.7)	41 (95.3)	0.002
AEDH, *n* (%)	18 (21.4)	11 (26.8)	7 (16.3)	0.24
ICH, *n* (%)	72 (85.7)	34 (82.9)	38 (88.4)	0.48
TSAH, *n* (%)	77 (91.7)	38 (92.7)	39 (90.7)	0.74
Treatment				
TXA, *n* (%)	41 (48.8)	19 (46.3)	22 (51.2)	0.66
FFP, median (IQR), mL	0 (0–720)	0 (0–280)	720 (0–1200)	0.01
Surgery, *n* (%)	51 (60.7)	12 (29.3)	39 (90.7)	< 0.001

Good outcome group, extended Glasgow Outcome Scale (GOS-E) of 5–8; *Poor outcome group*, GOS-E of 1–4

AEDH Acute epidural hematoma, *AIS* Abbreviated injury scale, *ASDH* Acute subdural hematoma, *FFP* Fresh frozen plasma, *GCS* Glasgow coma scale, *ICH* Intracerebral hematoma and contusion, *IQR* Interquartile range, *TSAH* Traumatic subarachnoid hemorrhage, *TXA* Tranexamic acid

vs. 90.7%, $p < 0.001$). No differences were found in the administration rates of TXA between the two groups.

Time courses of α2-PI and PIC

Figure 2 shows the time course of plasma α2-PI activities of all patients on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after TBI. The median plasma activity of α2-PI (normal range: 80–130%) did not change significantly from admission to 6 h after injury (1–3 h: t [83] = 1.89, difference [95% confidence interval (CI)]: 2.11 [− 0.08–4.30]%, $p = 0.06$; 3–6 h: t [83] = − 1.63, difference [95% CI]: − 1.71 [− 3.76–0.35] %, $p = 0.10$), and subsequently increased significantly from 6 h to 7 days after injury (6–12 h: t [83] = − 3.83, difference [95% CI]: − 4.36 [− 6.59–− 2.12] %, $p < 0.001$; 12 h–1 day: t [83] = − 6.60, difference [95% CI]: − 7.10 [− 9.21–− 4.99] %, $p < 0.001$; 1–3 days: t [74] = − 15.01, difference [95% CI]: − 16.97 [− 19.19–− 14.76] %, $p < 0.001$; 3–7 days: t [69] = − 10.58, difference [95% CI]: − 13.01 [− 15.43–− 10.59] %, $p < 0.001$).

Figure 3 shows the time course of plasma PIC levels of all patients on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after TBI. Plasma PIC levels (normal range: < 0.8 μg/mL) at admission were abnormally high in 82 (97.6%) of the 84 patients. The median plasma levels of PIC did not change significantly from admission to 3 h after injury (1–3 h: t [83] = − 1.19, difference [95% CI]: − 1.31 [− 3.48–0.86] μg/mL, $p = 0.24$), subsequently decreased significantly from 3 h to 1 day after injury (3–6 h: t [83] = 4.55, difference [95% CI]: 4.19 [2.38–5.99] μg/mL, $p < 0.001$; 6–12 h: t [83] = 7.98, difference [95% CI]: 6.99 [5.27–8.71] μg/mL, $p < 0.001$, 12 h–1 day: t [83] = 7.16, difference [95% CI]: 4.46 [3.24–5.68] μg/mL, $p < 0.001$). One to three days post-injury, it decreased, but not to a significant degree (1–3 days: t [74] = 0.29, difference [95% CI]: 0.03 [−0.21–0.28] μg/mL, $p = 0.77$). Subsequently, the PIC increased significantly from 3 to 7 days after injury (3–7 days: t [69] = − 7.42, difference [95% CI]: − 1.32 [− 1.68–− 0.97] μg/mL, $p < 0.001$).

α2-PI, PIC, and long-term outcome

We analyzed the time course of plasma α2-PI and PIC levels between the good and poor outcome groups by using GLMM with age, GCS score, presence of ASDH, and surgical intervention as covariates. The poor outcome group had significantly lower plasma α2-PI activity from the time of admission to 3 days post-injury, and significantly higher plasma PIC levels from admission to 6 h post-injury, compared to the good outcome group (Figs. 4 and 5).

α2-PI, PIC, and traumatic intracranial hemorrhage volume

Fifty-one patients who underwent surgery in the acute phase, two patients with segmentation errors in CT volumetry due to anatomical deviations such as large hematomas and brain edema, and one patient with an interval of more than six hours between the first and second CT scans were excluded from hematoma volume measurement. Finally, 30 patients (28 in the good outcome group and 2 in the poor outcome group) were included in this analysis (Table 2). The median hematoma expansion was 8.9 mL in the good outcome group and 55.9 mL in the poor outcome group (difference [95% CI]: − 47.0 [− 71.5–− 13.5] mL). There was no difference in the interval between CT scans between the two groups. We found a negative correlation between plasma α2-PI activity at admission and the change in hematoma volume (Fig. 6, Spearman's correlation coefficient, $r = -0.587$, $p = 0.001$).

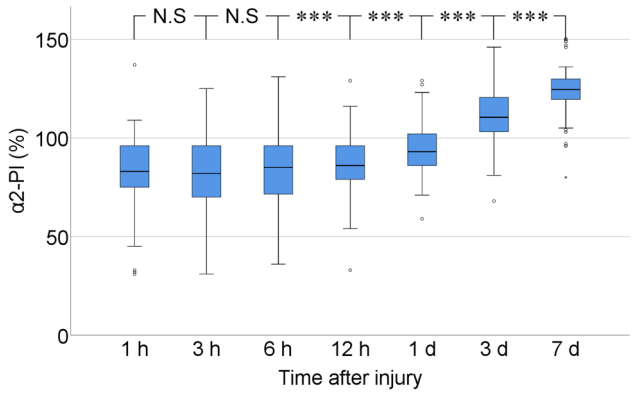

Fig. 2 Boxplots showing plasma levels of alpha 2-plasmin inhibitor (α2-PI) of all patients on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after traumatic brain injury. ***$p < 0.001$, N.S = Not Significant

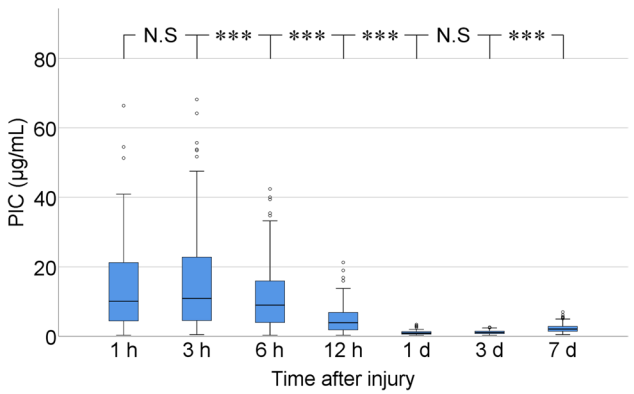

Fig. 3 Boxplots showing plasma levels of plasmin-alpha 2-plasmin inhibitor complex (PIC) of all patients on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after traumatic brain injury. ***$p < 0.001$, N.S = Not Significant

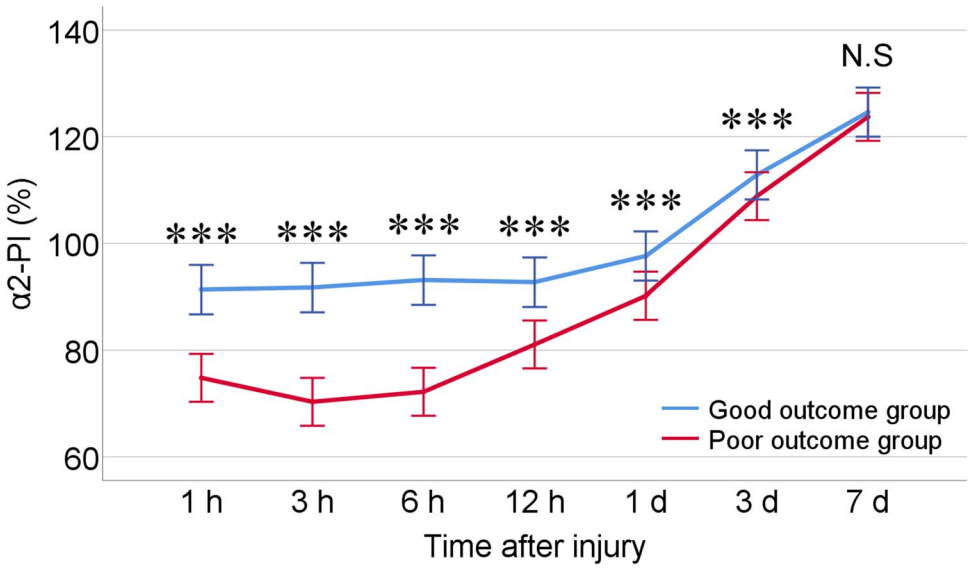

Fig. 4 Line graph showing plasma levels of alpha 2-plasmin inhibitor (α2-PI) of cases with good outcome and poor outcome on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after traumatic brain injury. Plasma α2-PI activities were significantly lower in the poor outcome group than in the good outcome group from the time of admission to 3 days post-injury, in the analysis using a generalized linear mixed model incorporating age, Glasgow Coma Scale score, presence of acute subdural hematoma, and surgical intervention as covariates. ***$p < 0.001$, N.S = Not Significant

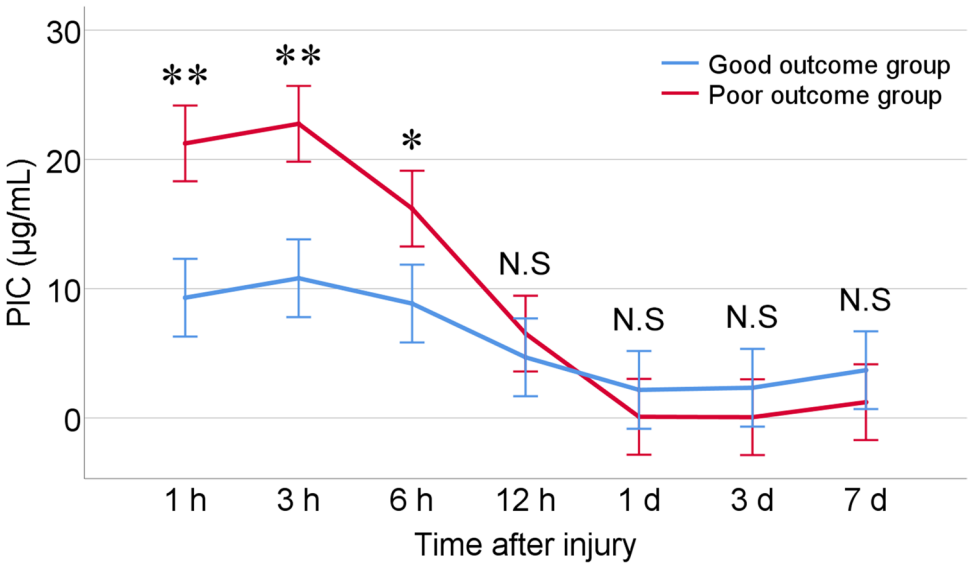

Fig. 5 Line graph showing plasma levels of plasmin-alpha 2-plasmin inhibitor complex (PIC) of cases with a good outcome and poor outcome on admission and 3 h, 6 h, 12 h, 1 day, 3 days, and 7 days after traumatic brain injury. Plasma levels of PIC were significantly higher in the poor outcome group than in the good outcome group from the time of admission to 6 h post-injury, in the analysis using a generalized linear mixed model incorporating age, Glasgow Coma Scale score, presence of acute subdural hematoma, and surgical intervention as covariates. *$p < 0.05$, **$p < 0.01$, N.S = Not Significant

No correlation was observed between plasma PIC levels at admission and the change in hematoma volume (Spearman's correlation coefficient, $r = 0.104$, $p = 0.58$).

α2-PI and PIC as independent risk factors for poor prognosis

Multiple logistic regression analysis was conducted to evaluate independent risk factors at admission associated with poor prognosis (Table 3). The explanatory variables included age [13, 28, 35], GCS score [23, 28, 35], presence of ASDH [23, 28, 35], surgical intervention [24, 31], and plasma levels of α2-PI and PIC. The response variable was defined as the outcome at 6 months post-injury, categorized as a good outcome (GOS-E 5–8) or a poor outcome (GOS-E 1–4). The analysis revealed that advanced age ($p = 0.002$), decreased GCS score ($p = 0.03$), surgical intervention ($p = 0.009$), and lower plasma α2-PI activity ($p = 0.04$) were independent predictors of poor prognosis.

Discussion

In this study, plasma PIC levels were abnormally elevated upon hospital arrival in most cases, indicating that plasmin was activated immediately after TBI, leading to enhanced fibrinolysis. Compared to the good outcome group, the poor outcome group exhibited lower α2-PI activity during the acute phase of TBI. α2-PI activity at admission was negatively correlated with hematoma expansion and served as an

Table 2 α2-PI, PIC, and changes in intracranial hematoma volume

	Total ($n = 30$)	Good outcome group ($n = 28$)	Poor outcome group ($n = 2$)	Difference (95% CI)
Hematoma volume at 1st CT scan, median (IQR), mL	9.7 (0.7–17.5)	9.7 (0.6–16.2)	47.2 (1.3–93.1)	−37.5 (−65.1 – −2.2)
Hematoma volume at 2nd CT scan, median (IQR), mL	20.2 (5.6–48.0)	20.2 (5.3–46.9)	103.1 (12.1–194.1)	−82.9 (−127.7 – −24.7)
Change in hematoma volume, median (IQR), mL	10.6 (2.3–26.0)	8.9 (2.2–25.1)	55.9 (10.8–101.0)	−47.0 (−71.5 – −13.5)
Interval between CT scans, median (IQR), minutes	163 (133–194)	163 (128–195)	160 (136–184)	3 (−69 – 80)
Plasma α2-PI activity on admission, median (IQR), %	91 (80–98)	92 (81–99)	82 (77–86)	10 (−11 – 31)
Plasma PIC level on admission, median (IQR), μg/mL	5.1 (2.5–9.4)	4.9 (2.4–8.3)	27.0 (13.0–40.9)	−22.1 (−30.7 – −11.0)

CT Computed tomography, *IQR* Interquartile range, *PIC* Plasmin-alpha 2-plasmin inhibitor complex, *α2-PI* Alpha 2-plasmin inhibitor

independent predictor of long-term outcome. These findings suggest that a reduction in α2-PI impairs fibrinolytic inhibition, further exacerbating the hyperfibrinolytic state, leading to hematoma enlargement and worse outcomes.

Increased plasma PIC levels indicate increased plasmin production and activation of fibrinolysis. It has been reported that after TBI, the conversion of plasminogen to plasmin is rapidly progressive as a result of release of large quantities of tPA from the injured endothelial cells [12, 18, 22]. Overproduction of plasmin consumes α2-PI. In the state of decreased α2-PI, plasmin is not sufficiently inactivated, and remains active in the blood. Under this condition, plasmin not only degrades fibrin immediately but also breaks down the critical coagulation factor fibrinogen, resulting in hypofibrinogenemia [25, 33]. In this study, the GLMM analysis showed that, in the poor outcome group, the α2-PI level was significantly lower up to 3 days post-injury, while the PIC level was significantly higher up to 6 h post-injury, compared to the good outcome group. These findings suggest that fibrinolytic activation may be involved in outcome deterioration. However, the results of the multiple logistic regression analysis indicated that α2-PI was an independent predictor of prognosis, whereas PIC was not a significant factor. Although PIC is a biomarker indicating the activation of fibrinolysis in the early phases of TBI, its association with prognosis could be confounded by factors such as the severity of TBI.

Based on the time course of PIC and α2-PI in this study, we demonstrated that fibrinolysis was activated immediately after TBI, with a peak occurring 3 h after injury, especially in the group with a poor long-term outcome. These results are consistent with our previous study, which examined the time course of fibrinolytic activity after TBI using fibrinogen and D-dimer [26, 27]. In these studies [26, 27], we investigated the time course of plasma fibrinogen and D-dimer levels after TBI, and showed that fibrinogen levels rapidly decrease within 3 h of injury, and D-dimer levels were abnormally elevated in most cases within 1 h of injury, peaked 3 h after injury. D-dimer is a fibrin degradation product that is produced after stabilized fibrin, which has been cross-linked by FXIIIa, is degraded by plasmin. Plasmin remains the main factor responsible for fibrinolysis, and this study has provided more evidence that in patients with a poor long-term outcome, the primary and secondary fibrinolysis mediated by plasmin and the disruption of fibrinolysis inhibition mediated by α2-PI rapidly progressed within 3 h of injury.

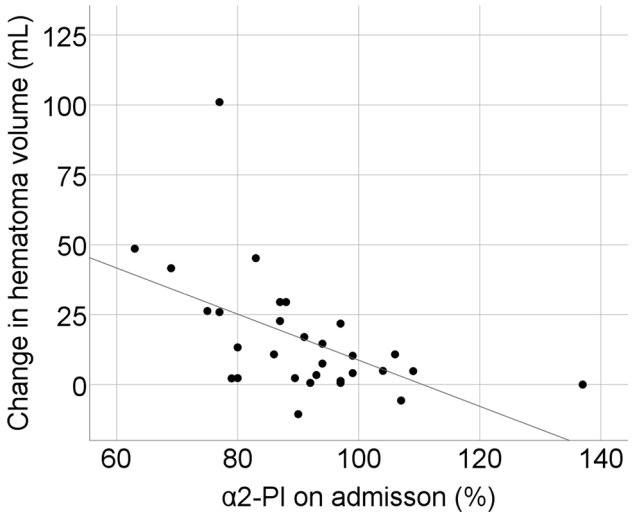

Fig. 6 Relationship between plasma alpha 2-plasmin inhibitor (α2-PI) activity at admission and changes in hematoma volume of the initial computed tomography (CT) scan upon admission and the follow-up CT scan. A negative correlation was observed between α2-PI activity at admission and the change in hematoma volume (Spearman's correlation coefficient, $r = -0.587$, $p = 0.001$)

Table 3 Multiple logistic regression analysis of initial variables as independent risk factors for poor prognosis

Factor	Odds Ratio (95% CI)	*p*
Age (10-y increments)	2.40 (1.37–4.20)	0.002
GCS score (1-point decrements)	1.30 (1.02–1.65)	0.03
ASDH	3.95 (0.18–85.84)	0.38
Surgery	19.4 (2.09–180.56)	0.009
α2-PI (10% decrements)	1.77 (1.04–3.04)	0.04
PIC (1 μg/mL increments)	1.04 (0.96–1.13)	0.32

$R^2 = 0.79$. *95% CI* 95% confidence interval, *ASDH* Acute subdural hematoma, *GCS* Glasgow coma scale, *PIC* Plasmin-alpha 2-plasmin inhibitor complex, *α2-PI* Alpha 2-plasmin inhibitor

Kushimoto et al.[20] reported that α2-PI activity decreased to < 60% within 3 h after injury in most of their poor outcome group 3 months after TBI injury, but the relationship between plasma α2-PI and long-term outcome was unclear. In our study, the poor long-term outcome group had lower α2-PI activity in the early phase of TBI compared to the good long-term outcome group. Additionally, α2-PI activity at admission was negatively correlated with hematoma expansion and served as an independent predictor of long-term outcome. This finding supports the concept that hyperfibrinolysis and hematoma expansion due to the disruption of fibrinolysis inhibition in the early phase of injury are associated with not only short-term but also long-term poor outcomes. In recent years, the effectiveness of TXA, an antifibrinolytic agent, in TBI patients has been demonstrated [3, 5]. However, a meta-analysis investigating the efficacy of TXA in TBI patients reported a reduction in mortality and hematoma expansion [4, 16, 37], while other studies suggest no impact on mortality [11]. The effectiveness of TXA in bleeding patients with coagulation disorders has been suggested to exhibit heterogeneity depending on the timing of administration, and its effects are not consistently recognized [6, 29]. Several studies [3, 5, 30] have shown that administering TXA during the phase when fibrinolysis is significantly elevated, particularly within 2–3 h after TBI, is associated with a reduction in mortality. The time course of PIC and α2-PI changes observed in this study also supports these results. Further research is needed to identify subgroups of patients who are most likely to benefit from TXA treatment.

Limitations

This study has several limitations. First, the sample size was relatively small, which did not provide sufficient power for statistical analysis. Second, α2-PI and PIC levels after 3 h post-injury could have been influenced by the administration of TXA or FFP or by surgery. Third, the semi-automatic analysis algorithm for CT volume measurement was unable to analyze two cases due to segmentation errors caused by anatomical deviations, such as large hematomas and brain edema. Additionally, in the follow-up CT scan, hematoma volume was underestimated in two cases due to decreased hematoma density. Finally, Japan has an aging population and the average age of TBI patients is high [38], which is likely partially responsible for the proportion of patients with poor outcome.

Conclusions

After TBI, the time course of plasmin revealed that fibrinolysis was activated immediately after injury, with a peak at 3 h after injury. Compared to the good outcome group, the poor outcome group not only had increased PIC levels but also decreased α2-PI activity during the acute phase of TBI. The reduction in α2-PI activity was correlated with hematoma expansion and poor outcomes, suggesting that less-inhibited hyperfibrinolysis may influence prognosis.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Central Ethics Committee of Nippon Medical School (Approval #M-2021–025, dated 16 February 2022) and the Ethics Committee of Kawaguchi Municipal Medical Center (Approval #2021–35, dated 7 March 2022).

Consent to participate This study was a retrospective study that used only information such as medical records and did not involve any invasion or intervention, therefore the requirement for obtaining informed consent was waived.

Consent to publish This study was a retrospective study that used only information such as medical records and did not involve any invasion or intervention, therefore the requirement for obtaining informed consent was waived.

Competing interests The authors declare no competing interests.

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