Original Article

Factors associated with the progression of traumatic intracranial hematoma during interventional radiology to establish hemostasis of extracranial hemorrhagic injury in severe multiple trauma patients

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Aim: To identify factors affecting the progression of traumatic intracranial hemorrhagic injury (t-ICH) during interventional radiology (IVR) for the hemostasis of extracranial hemorrhagic injury.

Methods: This was a retrospective comparative study. Fifty-two patients with t-ICH who underwent hemostasis using IVR for extracranial trauma at our institute were included. Clinical and computed tomography scan data were collected to investigate factors associated with t-ICH progression.

Results: Fifty-two subjects (36 men/16 women) with a mean age of 70.9 ± 19.2 years were analyzed. The mean Injury Severity Score was 34.9 ± 11.2. In 29 patients (55.7%), t-ICH progressed during IVR. Hematoma progression frequently occurred in patients with acute subdural hematoma (56.2%) and traumatic intracerebral hematoma/hemorrhagic brain contusion (66.6%). Factors associated with t-ICH progression included age ($P = 0.029$), consciousness level at admission ($P = 0.001$), Revised Trauma Scale ($P = 0.036$), probability of survival ($P = 0.043$), platelet count ($P = 0.005$), fibrinogen level ($P = 0.016$), hemoglobin level ($P = 0.003$), D-dimer level ($P = 0.046$), and red blood cell transfusion volume ($P = 0.023$).

Conclusion: Aggressive correction of anemia, thrombocytopenia, and low fibrinogen levels in severe consciousness disturbance patients with acute subdural hematoma and traumatic intracerebral hematoma/hemorrhagic brain contusion could improve the prognosis after IVR for hemostasis of extracranial hemorrhagic injuries.

Key words: Brain injury, consciousness, hemorrhagic shock, preventive measure

INTRODUCTION

SEVERE MULTIPLE TRAUMA is often accompanied by traumatic intracranial hemorrhagic injury (t-ICH). Notably, mortality rates increase approximately eight-fold among cases involving t-ICH concurrent with extracranial hemorrhagic trauma (e.g., massive hemothorax, intra-abdominal organ injury, and pelvic fracture), compared with head trauma alone.[1] In such concurrent cases, immediate hemostasis for extracranial hemorrhagic injury by interventional radiology (IVR) or surgery and the reversal of shock using fluid replacement and blood transfusion are the prioritized treatments. However, a t-ICH such as a brain contusion or traumatic intracranial hematoma could progress during treatment and worsen the patient's prognosis.

The progression of t-ICH during treatment could be attributable to the consumption of blood coagulation factors during persistent hemorrhage.[2,3] However, the specific characteristics and factors associated with the progression of t-ICH during IVR for the hemostasis of extracranial hemorrhagic injury remains unclear. Accordingly, this study analyzed predictive factors such as patients' background, symptoms, blood data, and clinical course, associated with t-ICH progression during IVR for hemostasis of extracranial hemorrhagic injuries.

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METHODS

WE UNDERTOOK A retrospective comparative study without negative criteria. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine at the University of Miyazaki (Miyazaki, Japan). Patient consent was obtained using an opt-out model.

Among 238 patients who had undergone hemostasis by IVR for extracranial hemorrhagic trauma between 1 April, 2012 and 31 March, 2019, 52 patients with t-ICH concurrent with extracranial hemorrhagic trauma were included (Fig. 1). "Severe multiple injuries" was defined as injuries at two or more sites and a score of 3 or higher on the Abbreviated Injury Scale (AIS 90 update 98).[4–6] "Traumatic intracranial hematoma" was defined as a traumatic acute epidural hematoma, acute subdural hematoma, traumatic intracranial hematoma (including hemorrhagic brain contusion), or traumatic subarachnoid hemorrhage evident on computed tomography (CT) scans.

Subjects were divided into either an enlarged or non-enlarged t-ICH group to investigate the frequency at which t-ICH enlargement occurred during IVR and the factors associated with its progression. Traumatic ICH enlargement was defined as: (i) an increase in an intracerebral hematoma or hemorrhagic brain contusion to 1.3 times the maximum size recorded during a previous CT scan, (ii) any increase (even slight) in an acute subdural hematoma or acute epidural hematoma relative to the maximum size recorded during a previous CT scan, (iii) an expanded distribution of traumatic subarachnoid hemorrhage. Two neurosurgeons blinded to the data (H. Ochiai and H. Okuyama) determined changes in t-ICH status based on CT scans and clinical symptoms. Computed tomography scans obtained at admission and immediately after IVR (i.e., within 30 min) were used in the analysis of each case. The change of systolic pressure during IVR was defined as the difference between systolic blood pressure after IVR and systolic blood pressure before IVR.

Data are presented as mean ± standard deviation. Statistical analysis was carried out using SPSS (version 23; IBM, Armonk, NY, USA). Group comparisons were undertaken

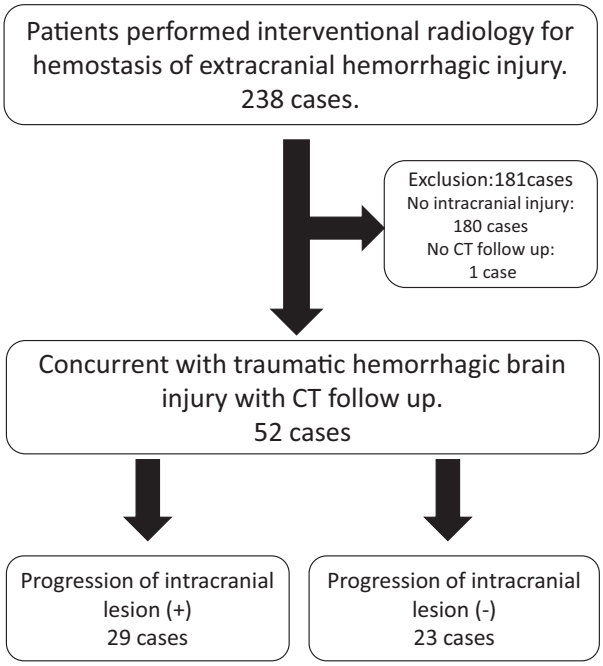

Fig. 1. Flow chart of patients in this study. CT, computed tomography.

Table 1. Baseline characteristics of patients with traumatic hemorrhagic brain injury who underwent interventional radiology to establish hemostasis of extracranial hemorrhagic injury

Age	70.9 ± 19.2 years
Gender	
Male	36
Female	16
Cause of injury	
Traffic accident	33
Fall	19
Type of intracranial injury	
Acute subdural hematoma	15
Acute extradural hematoma	14
Traumatic subarachnoid hemorrhage	3
Traumatic intracerebral hematoma/brain contusion	18
Intraventricular hemorrhage	3
Extracranial injury	
Face	2
Liver	7
Spleen	4
Kidney	3
Intestine/mesenterium	1
Unstable pelvic fracture	32
Intramuscular hemorrhage (gluteus, iliopsoas, femoral)	3
ISS	34.9 ± 11.2
RTS	6.49 ± 1.61
TRISS Ps	59.2 ± 31.5

Data are shown as number of cases or mean ± standard deviation.
ISS, Injury Severity Scale; RTS, Revised Trauma Score; TRISS Ps, Trauma and Injury Severity Score probability of survival.

using the Mann–Whitney *U*-test and χ^2-test. Multivariate analysis was carried out using logistic regression. The significance criterion was set at a *P*-value < 0.05.

RESULTS

THE BASELINE CHARACTERISTICS of the cases are shown in Table 1. The subjects had a mean Injury Severity Scale score of 34.9 ± 11.2, mean Revised Trauma Score (RTS) of 6.49 ± 1.61, and mean Trauma Injury and Severity Score Probability of survival (TRISS Ps) of 59.2 ± 31.5. Extracranial injuries requiring hemostasis by IVR were observed in 32 cases of pelvic fracture, 15 cases of abdominal organ injury, three cases of gluteal muscle hematoma, and two cases of facial trauma. The frequency of t-ICH progression during IVR and the associated factors are shown in Table 2. Twenty-nine cases (55.7%) showed t-ICH progression during IVR. Age ($P = 0.029$), consciousness level (i.e., Glasgow Coma Scale [GCS]) at admission ($P = 0.001$), RTS ($P = 0.036$), TRISS Ps ($P = 0.043$), platelet count ($P = 0.005$), fibrinogen level ($P = 0.016$), D-dimer level ($P = 0.046$), hemoglobin level ($P = 0.003$), and red blood cell transfusion volume differed significantly between the patients with enlarged or non-enlarged t-ICH. The cut-off values of these factors are shown in Table 3. Age and GCS scores were significantly correlated with the enlarged t-ICH group ($r = -0.405$, $P = 0.029$) but not with the non-enlarged t-ICH group ($r = 0.162$, $P = 0.47$). There were no significant group differences in AIS (chest), AIS (abdomen) scores, Japan Association of Acute Medicine disseminated intravascular coagulation scores or changes in systolic blood pressure during IVR (Table 2). There was no significant difference in changes in systolic blood pressure during IVR in each group. Finally, there was no significant group difference in pre-injury antithrombotic therapy (Table 4).

Table 2. Comparison of severe multiple trauma patients with enlarged or non-enlarged traumatic intracranial hemorrhagic injury (t-ICH), by multivariate logistic regression analysis

	Enlarged t-ICH (*n* = 29)	Non-enlarged t-ICH (*n* = 23)	*P*-value
Age (years)	73.6 ± 18.9 (28–99)	66.0 ± 19.6 (17–85)	0.020
ISS	34.3 ± 12.1 (12–68)	34.5 ± 10.8 (13–57)	n.s.
GCS	9.55 ± 4.4 (3–15)	12.73 ± 3.1 (6–15)	0.001
RTS	5.98 ± 1.88 (2.3–7.8)	7.16 ± 0.82 (5.6–7.8)	0.036
TRISS Ps (%)	50.3 ± 34.6 (0.8–98.4)	70.9 ± 22.6 (14.4–97.4)	0.043
JAAM-DIC score	4.4 ± 1.6 (2–9)	4.0 ± 1.7 (1–5)	n.s.
AIS (chest)	2.3 ± 1.7	1.9 ± 1.5	n.s.
AIS (abdomen)	3.4 ± 0.9	3.3 ± 1.1	n.s.
sBP (mmHg)	113.4 ± 34.2 (55–171)	111.7 ± 24.8 (53–152)	n.s.
Heart rate (b.p.m.)	95.8 ± 24.2 (50–146)	94.5 ± 20.6 (56–139)	n.s.
SpO_2 (%)	96.9 ± 6.6 (69–100)	96.9 ± 4.1 (83–100)	n.s.
Lactate (mmol/L)	5.67 ± 14.22 (1.5–16.6)	4.56 ± 4.22 (0.24–15.99)	n.s.
Platelets (10^3/μL)	120.7 ± 46.9 (20–220)	165.1 ± 53.6 (73–257)	0.005
Hemoglobin (g/dL)	9.079 ± 2.5 (3.9–14.5)	11.432 ± 2.0 (6.1–14.2)	0.003
Fibrinogen (mg/dL)	131.5 ± 77.9 (27–286)	197.4 ± 63.7 (82–315)	0.016
FDP (μl/mL)	317.9 ± 448.2 (26.7–916.5)	209.6 ± 157.6 (42–587)	n.s.
D-dimer (μl/mL)	198.5 ± 155.5 (14.86–542.5)	117.3 ± 84.37 (5.93–323.3)	0.046
Transfused RBC/RCC (U)	9.2 ± 8.3 (0–30)	5.2 ± 5.6 (0–20)	0.023
Transfused FFP (U)	8.6 ± 8.2 (0–30)	6.2 ± 5.8 (0–25)	n.s.
Transfused PC (U)	5.17 ± 9.4 (0–40)	1.8 ± 3.9 (0–10)	n.s.
Time from injury to IVR (min)	212.4 ± 121.4 (1–466)	309.0 ± 78.5 (120–1380)	n.s.
Change of sBP during IVR (mmHg)†	−3.4 ± 32.2 (−50 to 73)	11.4 ± 22.1 (−20 to 59)	n.s.

Data are presented as mean ± standard deviation.
†Defined as systolic blood pressure (sBP) after interventional radiology (IVR) minus sBP before IVR.
AIS, Abbreviated Injury Scale; FDP, fibrin degradation product; FFP, flesh frozen plasma; GCS, Glasgow Coma Scale; ISS, Injury Severity Scale; JAAM-DIC, Japan Association of Acute Medicine – Disseminated Intravascular Coagulation; n.s.: not significant; PC, platelet concentrate; RBC, red blood cell concentrate; RCC, red cell concentrate; RTS, Revised Trauma Score; TRISS Ps, Trauma and Injury Severity Score probability of survival.

Table 3. Cut-off values of factors affecting enlargement of traumatic intracranial hemorrhagic injury during interventional radiology to establish hemostasis of extracranial hemorrhagic injury

Factor	Cut-off value	AUC	95% CI	Sensitivity	Specificity	*P*-value
Hemoglobin (g/dL)	11.0	0.784	0.651–0.918	0.862	0.727	0.001
Fibrinogen (mg/dL)	160	0.754	0.617–0.891	0.714	0.789	0.003
GCS	13	0.731	0.594–0.869	0.379	0.273	0.005
Platelets (10^3/μL)	157.5	0.724	0.582–0.866	0.138	0.455	0.007
Age (years)	80.5	0.679	0.533–0.826	0.517	0.864	0.029
RTS	5.45	0.667	0.519–0.815	0.655	0.001	0.043
TRISS Ps (%)	57.5	0.667	0.518–0.816	0.414	0.227	0.043
D-dimer (μl/mL)	82	0.647	0.492–0.801	0.793	0.45	n.s.
Transfused RBC/RCC (U)	10	0.637	0.484–0.791	0.379	0.909	n.s.

AUC, area under curve; CI, confidence interval; GCS, Glasgow Coma Scale; n.s., not significant; RBC, red blood cell concentrate; RCC, red cell concentrate; RTS, Revised Trauma Score; TRISS Ps, Trauma and Injury Severity Score probability of survival.

Table 4. Pre-injury antithrombotic agent use in patients with enlarged or non-enlarged traumatic intracranial hematoma (t-ICH) during interventional radiology to establish hemostasis of extracranial hemorrhagic injury

Pre-injury antithrombotic agent use	Enlarged t-ICH	Non-enlarged t-ICH
Yes	3	7
No	16	11
Unknown	10	5

In a subgroup analysis, according to the elapsed time from injury to IVR (i.e., the time from injury to needle puncture for IVR), 26 subjects underwent IVR within 3 h post-injury. In those cases, the platelet count ($P = 0.01$) and D-dimer ($P = 0.04$), hemoglobin ($P = 0.002$), and fibrin degradation product levels ($P = 0.04$) were associated with t-ICH expansion. The remaining 26 subjects underwent IVR more than 3 h post-injury. In those cases, GCS scores at admission and fibrinogen levels were associated with t-ICH expansion (Fig. 2).

Next, we undertook a subgroup analysis according to the type of t-ICH. Hematoma progression was observed in 40.0% of traumatic subarachnoid hemorrhage cases, 56.2% of acute subdural hematoma cases, 50.0% of acute epidural hematoma cases, and 66.6% of traumatic intracerebral hematoma/hemorrhagic brain contusion cases. In the acute subdural hematoma and traumatic intracerebral hematoma/hemorrhagic brain contusion subgroups, age ($P = 0.02$), platelet count ($P = 0.04$), fibrinogen level ($P = 0.003$), hemoglobin level ($P = 0.002$), and time from injury to the start of IVR ($P = 0.03$) were associated with t-ICH progression (Table 5, Fig. 3). In the subarachnoid hemorrhage and intraventricular hemorrhage subgroup, only hemoglobin level ($P = 0.03$) was associated with t-ICH progression (Table 5, Fig. 4).

DISCUSSION

IN THIS STUDY, we identified age, GCS scores at admission, RTS, TRISS Ps, platelet, hemoglobin, D-dimer levels, fibrinogen levels, and red blood cell transfusion volume as factors significantly associated with t-ICH enlargement during IVR. The cut-off values of fibrinogen level and platelet count were 160 mg/dL and 157.5 × 10^3/μL, respectively. Previous reports suggested that the fibrinogen level and platelet count should be kept normal in patients with traumatic coagulopathy.[7] Our results are consistent with those previously reported, and these values could be useful indicators for predicting t-ICH enlargement during IVR. Moreover, in our study we found that the cut-off value of the D-dimer level was 82.0 μg/mL. In isolated traumatic intracranial hematoma progression, Nakae *et al.*[8] reported that the cut-off value of the D-dimer level was 37.5 μg/mL. Our result was nearly twice as high as this. A possible reason for this is that, in our study, extracranial hemorrhage and bone fractures could modify the value. Age was considered to be a highly specific index for the enlargement of t-ICH. Finally, we identified a high frequency of t-ICH enlargement in patients with acute subdural hematoma and traumatic intracerebral hematoma/hemorrhagic brain contusion.

Traumatic ICHs could enlarge over time. For example, Narayan *et al.* compared CT scans of patients with t-ICH

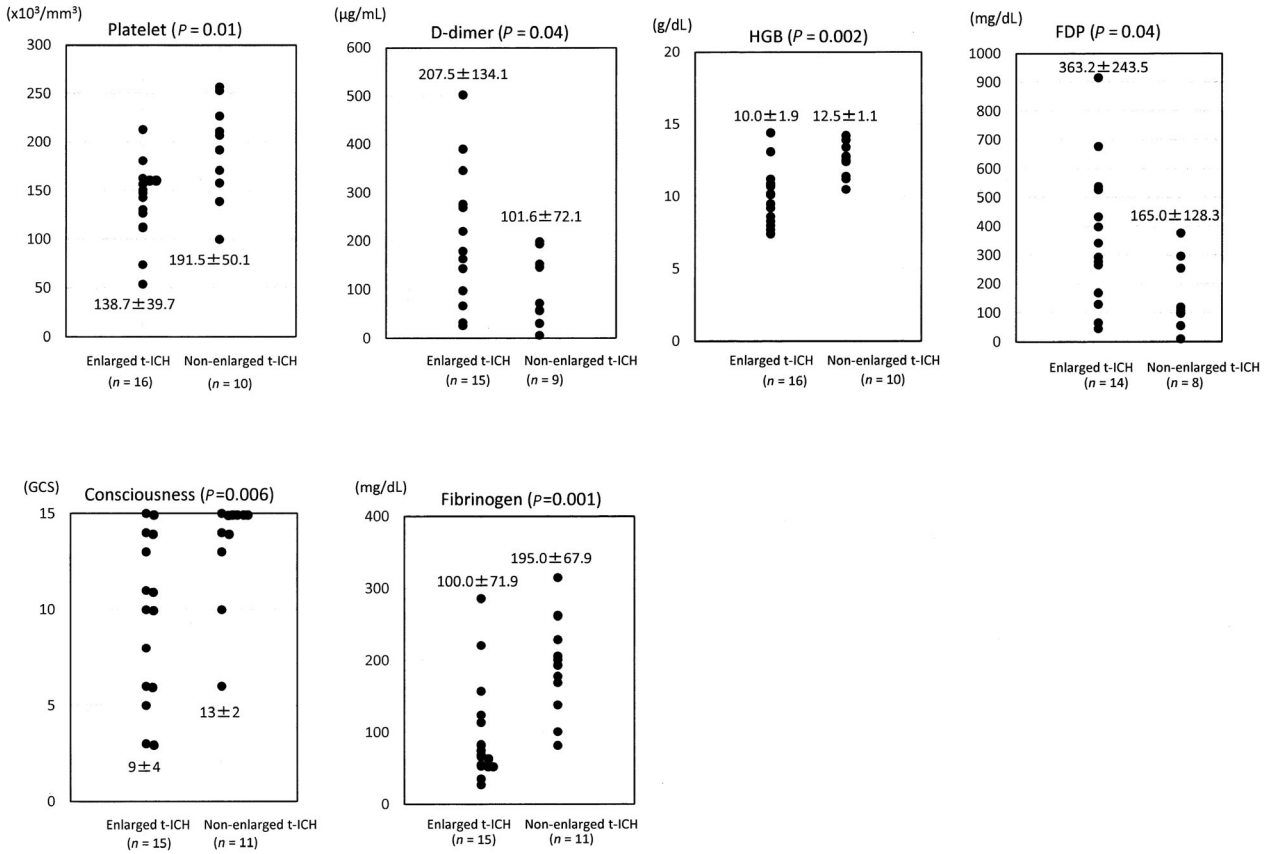

Fig. 2. Factors affecting the progression of traumatic intracranial hemorrhagic lesions (t-ICH). Top panels: Cases in which interventional radiology for the hemostasis of extracranial hemorrhagic injury was initiated within 3 h post-injury (n = 26; 16 cases of enlarged t-ICH and 10 cases of non-enlarged t-ICH). Bottom panels: Cases in which interventional radiology for the hemostasis of extracranial hemorrhagic injury was initiated more than 3 h post-injury (n = 26; 15 cases of enlarged t-ICH and 11 cases of non-enlarged t-ICH). FDP, fibrin degradation product; HGB, hemoglobin.

Table 5. Comparison of enlarged and non-enlarged traumatic intracranial hematoma (t-ICH) in patients with acute subdural hematoma (SDH)/contusion and subarachnoid hemorrhage/intraventricular hemorrhage (SAH/IVH)

	Enlarged t-ICH	Non-enlarged t-ICH	*P*-value
Acute SDH/contusion			
Age (years)	77.1 ± 15.9	67.5 ± 18.1	0.020
Platelet count (10^3/μL)	117.0 ± 43.9	162.5 ± 62.6	0.040
Fibrinogen (mg/dL)	117.0 ± 70.1	191.1 ± 61.7	0.003
Hemoglobin (g/dL)	8.8 ± 2.0	11.2 ± 2.2	0.002
Time from injury to IVR (min)	182.2 ± 81.4	318.3 ± 194.5	0.030
SAH/IVH			
Hemoglobin (g/dL)	8.6 ± 3.1	11.4 ± 1.7	0.030

IVR, interventional radiology.

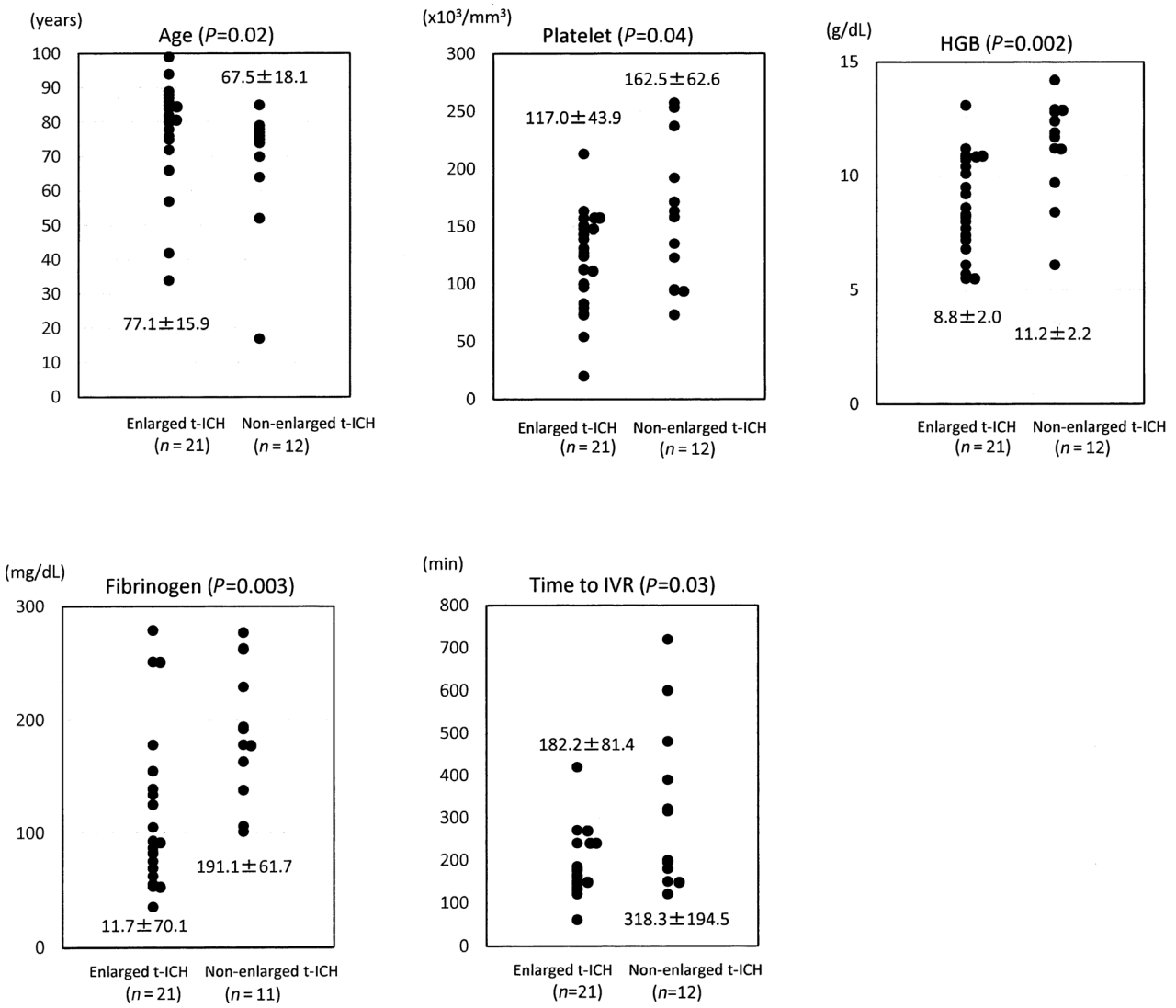

Fig. 3. Subgroup analysis of age, platelet count, hemoglobin, fibrinogen, and time from injury to interventional radiology (IVR) in patients with acute subdural hematoma/contusion with and without hematoma progression (n = 33; 21 cases of enlarged traumatic intracranial hemorrhagic lesion [t-ICH] and 12 cases of non-enlarged t-ICH). HGB, hemoglobin.

obtained at admission and 24 h post-injury and reported that 50% showed progression during that time interval.[9] Similarly, Sifri *et al.*[10] reported that 15% of patients with t-ICH showed enlargement of the hematoma without progression of neurological symptoms. Other studies observed that progression occurred in 60% of patients with hemorrhagic brain contusion[11] and that enlargement occurred in 17% of patients with acute subdural hematoma.[12] We observed that 56.2% and 66.6% of patients with acute subdural hematoma and traumatic intracerebral hematoma/hemorrhagic brain contusion, respectively, showed hematoma progression during IVR. These t-ICH subtypes could indicate a high risk of hematoma progression during IVR for the hemostasis of extracranial hemorrhagic injury in severe multiple trauma patients.

The high frequency of hematoma progression in patients with traumatic brain injury/hemorrhagic brain contusion might be related to the release of tissue factors from the damaged brain. Previous reports have proposed mechanisms of traumatic intracranial hematoma/hemorrhagic brain contusion progression in patients with head trauma alone.[13–17] In isolated traumatic brain injuries, the hyperfibrinolytic

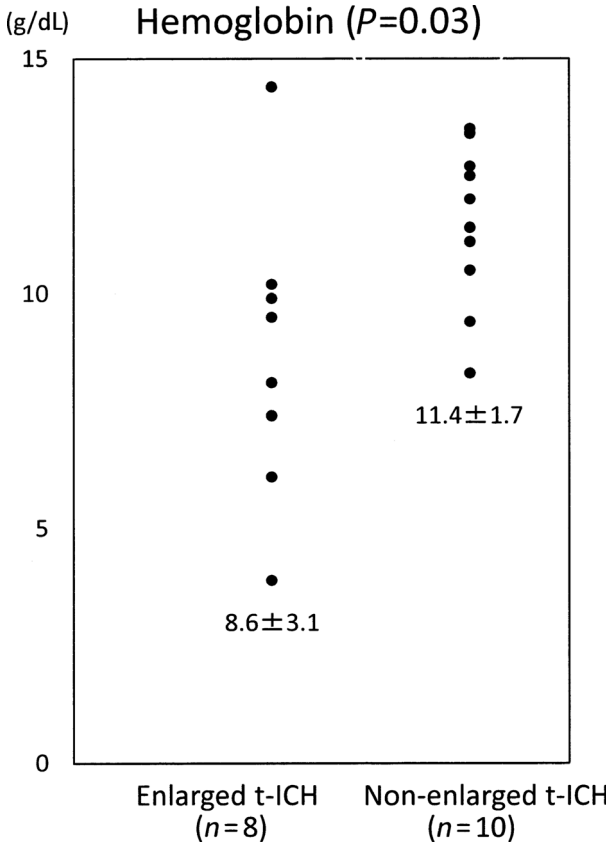

Fig. 4. Subgroup analysis of hemoglobin levels in patients with traumatic subarachnoid hemorrhage/intraventricular hemorrhage with and without hematoma progression (n = 18; 8 cases of enlarged traumatic intracranial hemorrhagic lesion [t-ICH] and 10 cases of non-enlarged t-ICH).

state evoked by a brain injury was related to tissue factors released into the blood, microvessel failure, disruption of the blood–brain barrier, platelet–endothelial interaction, and platelet dysfunction.[18–20] These conditions activated the blood coagulation system and increased the consumption of blood coagulation factors. Additionally, the release of endogenous plasminogen activator was evoked and hyperfibrinolysis occurred.[18–20] Biomarkers to predict progressive hemorrhagic brain injury in isolated traumatic brain injury have been reported reflecting these responses.[8,21] Nakae *et al.* reported that D-dimer was an important biomarker to predict progressive hemorrhagic brain injury in isolated traumatic brain injury, reaching a peak at 3 h after injury before returning to baseline.[8,21] Based on these reports, we divided our group into "within 3 h" (peak fibrinolysis phase) and "beyond 3 h" (post-fibrinolytic phase) after injury.

Conversely, when the hemorrhagic state is concurrent with a traumatic injury, the following factors might modify the hyperfibrinolysis state: loss of blood coagulation factor by hemorrhage, consumption of blood coagulation factor induced by cross-talk between endothelial inflammation and the coagulation system, activation of protein C by thrombomodulin, and the dilution of blood coagulation and hypothermia by fluid resuscitation.[18–20,22] In our study, in the group who received IVR within 3 h, fibrin degradation product and D-dimer were associated with the progression of hemorrhagic brain injury. However, in the group who received IVR after 3 h, fibrinogen and GCS were the associated factors. This result might reflect the fact described above. Another study reported that treatment with factor VII (prothrombin complex concentrate) alleviated progressive brain contusions.[23] Platelet transfusion, anticoagulant therapy, and blood pressure have all been identified as factors related to the enlargement of acute subdural hematoma.[24] In our study, we identified the platelet count and D-dimer level in IVR within 3 h, as well as fibrinogen level and GCS scores in cases where IVR was delayed by more than 3 h post-injury, as factors associated with t-ICH progression. Our results suggest that the breakdown of hemostasis and coagulation due to extracranial hemorrhagic trauma enhanced the abnormalities in local blood coagulation induced by head trauma.

We also identified hemoglobin level as a factor associated with t-ICH progression. This potentially reflects the development of anemia, reducing the axial flow in the arterioles, and thus inhibiting platelets from passing near the blood vessel walls.[25–27] Consequently, the ability of platelets and endothelial cells to form adhesive or aggregative interactions would be reduced, and hemostasis would be attenuated. Additionally, red blood cells usually enhance blood coagulation by expressing anticoagulant phospholipids and releasing ADP to promote the production of thromboxane A2 and thrombin by platelets and factor IX activation on activated platelets. However, these effects are attenuated by a decrease in the hemoglobin level, resulting in an increased bleeding tendency.

Regarding consciousness, our observation of a 1.5-fold increase in the risk of t-ICH progression with every 1-point decrease in GCS emphasizes that strict observation of the patient's consciousness level is vital in this context. We also found a significant correlation between age and GCS. This observation might reflect the fact that the aged brain is vulnerable to injury and prone to coagulopathy when injured.[28,29] Patients with severe consciousness disturbance at admission are at a high risk for progression of t-ICH. However, patients with multiple trauma who require IVR for the hemostasis of extracranial trauma often develop hemorrhagic shock and require endotracheal intubation and sedation. Therefore, it could be difficult to monitor changes in

consciousness during IVR. Potentially, continuous pupil monitoring using a quantitative pupilometer[30] and cone-beam CT imaging during IVR could resolve this problem. Based on our findings, in order to improve the prognosis of patients with acute subdural hematoma/hemorrhagic brain contusion who require IVR, clinicians must be aware that patients with severe consciousness disturbance at admission are at a high risk for t-ICH progression and require careful monitoring during the procedure and to ensure the aggressive correction of anemia, thrombocytopenia, and low fibrinogen levels.

This study has a few limitations. The number of cases was relatively small, and the study was carried out at a single institution. A multicenter study with a larger number of cases could be required to confirm our results. Additionally, as the timing of blood collection in this study was not immediately before the start of IVR, treatments up to the start of IVR might have modified blood parameters.

CONCLUSION

IN THIS RETROSPECTIVE study, we evaluated potential factors affecting t-ICH progression during IVR for the hemostasis of hemorrhagic extracranial injuries. To improve the prognosis of patients with acute subdural hematoma/hemorrhagic brain contusion who require IVR, clinicians should be aware that patients with severe consciousness disturbance are at high risk for t-ICH progression, requiring careful monitoring of consciousness during the procedure, and ensure the aggressive correction of anemia, thrombocytopenia, and low fibrinogen levels.

DISCLOSURE

APPROVAL OF THE research protocol: The protocol for this research project was approved by a suitably comprised institutional Ethics Committee and conformed to the provisions of the Declaration of Helsinki (University of Miyazaki, Approval No. O-0220).

Informed consent: Informed consent was obtained from the subjects or guardians in an opt-out model involving publicity documents.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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