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ORIGINAL RESEARCH

Time-Dependent Association of Preinjury Anticoagulation on Traumatic Brain Injury-Induced Coagulopathy: A Retrospective, Cohort Study

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ABSTRACT

Background and objectives: The impact of preinjury anticoagulation on coagulation parameters over time after traumatic brain injury (TBI) has remained unclear. Based on the hypothesis that preinjury anticoagulation significantly influences the progression and persistence of TBI-induced coagulopathy, we retrospectively examined the association of preinjury anticoagulation with various coagulation parameters during the first 24 hours postinjury in 5 periods. **Methods:** Data from the registry of patients with TBI aged ≥65 years admitted between 2019 and 2023 were used. Time since injury was classified into 5 categories through a graphical analysis of coagulation parameters. We examined the association between preinjury anticoagulation and the platelet count, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), D-dimer level, and fibrinogen level during each period by analysis of covariance using 10 clinical factors as confounding factors. **Results:** Data from 545 patients and 795 blood tests were analyzed. The patients' mean age was 78.9 years, and 87 (16%) received anticoagulation therapy. The preinjury anticoagulation group had significantly greater Rot- terdam computed tomography scores and poorer outcomes at discharge than the control group, with significantly lower D-dimer levels and higher fibrinogen levels. Analysis of covariance revealed significant associations be- tween the D-dimer level and preinjury anticoagulation within 2 to 24 hours postinjury, APTT and preinjury anticoagulation within 1 to 24 hours, and PT-INR and preinjury anticoagulation throughout all periods up to 24 hours postinjury. **Conclusion:** Despite more severe TBI signs and poorer outcomes, the preinjury anticoagulation group had signif- icantly lower D-dimer levels, especially within 2 to 24 hours postinjury. Thus, D-dimer levels during this period may notreliably represent TBI severity in patients receiving anticoagulation therapy before injury. Preinjury anticoagulation wasalso associated with an elevated PT-INR and prolonged APTT from early to 24 hours postinjury, highlighting the im- portance of aggressive anticoagulant reversal early after injury.

Key words: Anticoagulants, Antithrombins, Blood coagulation disorders, Cohort studies, Fibrin fragment D, Traumatic brain injury

Preinjury anticoagulation has a significant impact on the outcome of patients with trauma.[1] Specifically, in the context of traumatic brain injury (TBI), the preinjury use of vitamin K antagonists (VKAs) has been associated with in- creased mortality and a higher incidence of neurosurgical inter- ventions.[2] Direct oral anticoagulants (DOACs) are generally known to cause fewer hemorrhagic complications than VKAs; however, previous research has demonstrated no significant dif- ference in in-hospital mortality or progression of intracranialhemorrhage (ICH) between patients with TBI receiving DOACs and those receiving VKAs.[3,4] In clinical practice, patients with TBI receiving anticoagulants, even DOACs, are often prone to increased bleeding.[5] A few studies have suggested an association between elevation of the prothrombin time-international normal- ized ratio (PT-INR) and prolongation of the activated partial thromboplastin time (APTT) because of preinjury anticoagulation. However, the specific time course after injury has not been ex- amined, nor has the D-dimer level, a clinical severity marker.[6] Therefore, we hypothesized that preinjury anticoagulation agents, including DOACs, significantly affect the progression and persis- tence of TBI-induced coagulopathy. To confirm this hypothesis, we investigated the effects of preinjury anticoagulation therapy on various coagulation parameters within the first 24 hours postinjury,categorized into 5 time periods.

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METHODS

Setting and Participants

In this retrospective, multicenter cohort study, we analyzed clinical data from a prospective registry of patients aged ≥65 years admitted to Saraswathi Institute of Medical Sciences for acute treatment of TBI from December 2019 to May 2021.[7] The requirement for patient consent was waived because of the observational nature of the study. The sample size was defined by the number of patients enrolled in the registry and was designed to be larger than previous studies examining temporal trends in TBI-induced coagulopathy and the influence of preinjury anticoagulant therapy.[6,8] The reporting of this study conforms to the Standards for Reporting of Observational Studies in Epidemiology guidelines.[9]

Variables

The collected data comprised 38 clinical factors, including age, preinjury antiplatelet and anticoagulant use, times from injury to arrival and blood testing, physical findings at arrival, plasma coagulation parameters (platelet count, PT-INR, APTT, D-dimer level, and fibrinogen level), computed tomography (CT) findings, and information on treatment and outcomes at discharge. A detailed description and definitions of these factors are provided in Supplemental Digital Content 1 (http://links.lww.com/NEU/E532). Missing values for clinical factors, excluding coagulation parameters, preinjury anticoagulation, and treatment and outcome information, were imputed using the k-nearest neighbor method.[10] The data from the first, second, third, and fourth blood sampling sessions were compiled into separate timepoint datasets for comprehensive analysis.

Outcomes and Exposures

The primary outcome was the plasma levels of the following coag- ulation parameters: platelet count, PT-INR, APTT, D-dimer, and fi- brinogen. The exposure was defined as preinjury anticoagulation.

Graphical Analysis

Scatter plots were generated with some stratifications for coagulation parameters and time since injury. We then plotted polynomial regression curves optimized for the R2 score. These details are provided in Sup-plemental Digital Content 1 (http://links.lww.com/NEU/E532).

Univariate Analysis

Before analysis of covariance (ANCOVA), the following 10 relevant predictors were evaluated by univariate analysis to identify potential con- founders: total Glasgow Coma Scale (GCS) score, presence of bilateral fixed dilated pupils, Rotterdam CT score, occurrence of massive cerebral contusion or traumatic ICH, systolic blood pressure, skull base fracture, age, preinjury modified Rankin scale (mRS) score, tranexamic acid (TXA) administration, and anticoagulation reversal. Each of these factors was selected for its clinical relevance, which is detailed in Supplemental Digital Content 1 (http:// links.lww.com/NEU/E532). Factors significantly associated with coagulation parameters were used as potential confounders for subsequent ANCOVA.

ANCOVA

ANCOVA was conducted only for the postinjury time category, in which a significant association between preinjury anticoagulation and coagulation parameters was observed. Similarly, only potential confounders that showed a significant association with coagulation parameters in the univariate analysis were subjected to ANCOVA.

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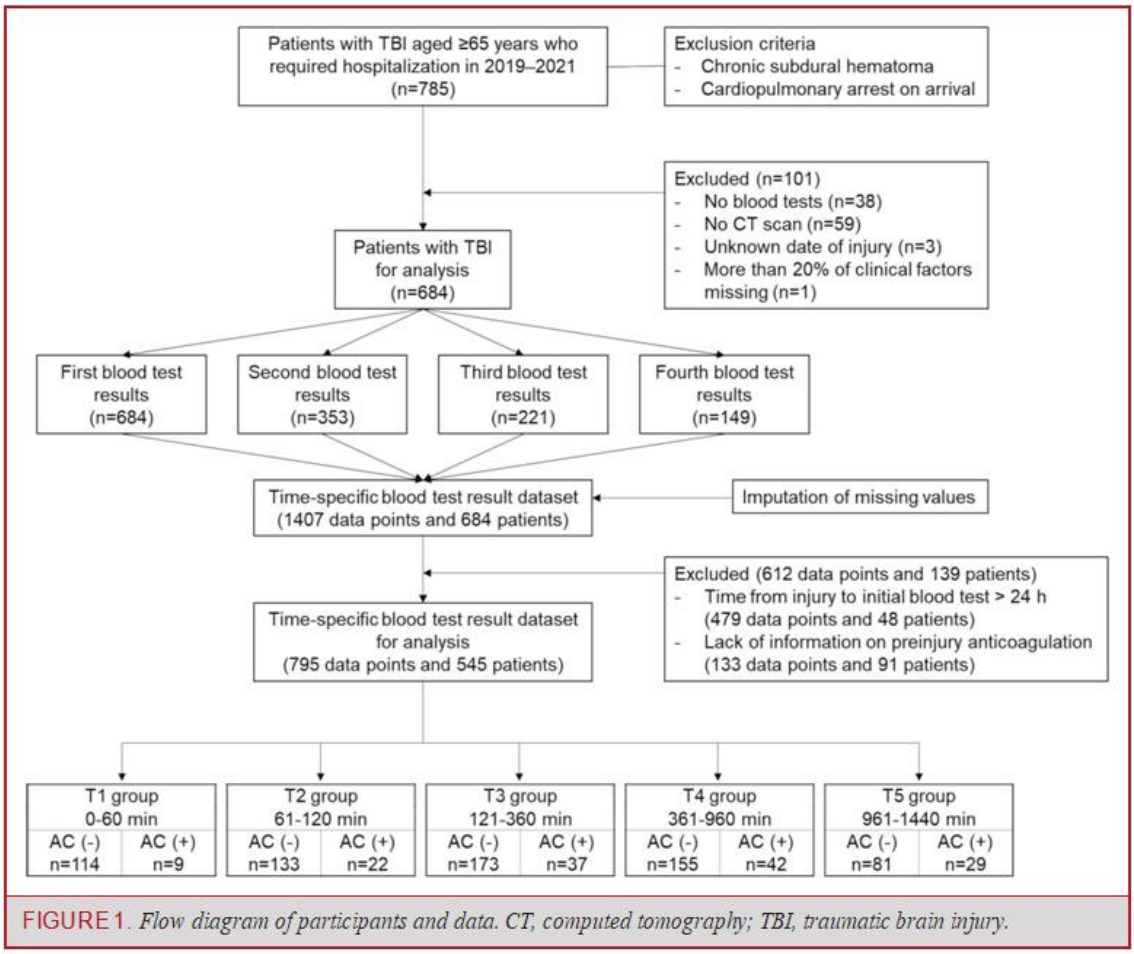

FIGURE 1. *Flow diagram of participants and data. CT, computed tomography; TBI, traumatic brain injury.*

Statistics

In all the aforementioned analyses, D-dimer level and age were log- transformed, whereas platelet count, PT-INR, APTT, fibrinogen level, Rotterdam CT score, GCS score, and preinjury mRS score underwent exponential transformations through R function powerTransform for normal distribution approximation.[11] Fisher exact, Mann-Whitney *U*, and *t* tests were used to compare patient backgrounds between groups. For Mann- Whitney *U* test comparisons, the bootstrap method was used to calculate 95% CIs for median differences. In the univariate analysis, nominal variables were analyzed by *t* tests and continuous variables by univariate regression. When calculating 95% CIs for exponentially transformed variables, negative values cannot be retransformed into interpretable values. Therefore, the bootstrap method was used to calculate the 95% CIs of the mean differences between groups for coagulation parameters by the postinjury period. When using exponentially transformed variables in ANCOVA and univariate re- gression analysis, presenting interpretable CIs is challenging because of the difficulty of rescaling the calculated CIs. Consequently, 95% CIs were not reported in these analyses. $P < .05$ was considered statistically significant. Statistical analyses were performed using EZR version 1.54 (R version 4.0.3). The Python library scikit-learn version 1.2.2 was used in Python 3.9 to impute missing values and optimize the polynomial regression curves.[12] Data supporting the study's findings are available from the corresponding author upon reasonable request.

Sensitivity Analysis

A sensitivity analysis was performed by excluding outliers, changing the imputation method for missing values, changing the univariate analysis method, and stratifying the GCS data.

RESULTS

Data Preparation Process

A flow diagram of the patient data is presented in Figure 1. After excluding ineligible data from 785 TBI patients in the multicenter registry and imputing missing values, the final dataset for analysis included 545 patients and 795 distinct time-specific data points.

Patients

The clinical characteristics of the 545 patients are detailed in Supplemental Digital Content 2 (http://links.lww.com/NEU/ E533). Their mean age was 78.9 years, and 344 (63.1%) were male. The median time from injury to the initial blood test was 119 minutes. Eighty-seven (16.0%) patients received anticoagulants

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TABLE 1. Patients' Background and Clinical Characteristics in the Two Groups

Variables	Control group n = 458	Preinjury anticoagulation group n = 87	*P* value[a]	95% CI[b]
Age, y	78.3 ± 7.6	82.1 ± 6.8	<.001	0.85-0.93
Male sex	286 (62.4)	58 (66.7)	.47	0.72-2.03
Preinjury mRS score	0 [0-1.8]	1 [0-2]	.008	0-1
Preinjury mRS score of >3	30 (6.8)	10 (11.8)	.12	0.75-3.93
Injury to arrival time, min	63.5 [40-180]	123 [60-518]	<.001	26.0-162
Injury to blood test time, min	105 [61-226]	165 [99-531]	<.001	24.5-151
Postinjury time period categories, min				
0-60	114 (24.9)	9 (10.3)	.002	0.15-0.73
61-120	133 (29.0)	22 (25.3)	.52	0.47-1.43
121-360	133 (29.0)	30 (34.5)	.31	0.76-2.14
361-960	56 (12.2)	18 (20.7)	.04	0.97-3.46
961-1440	22 (4.8)	8 (9.2)	.12	0.74-4.88
Alcohol positive	38 (8.3)	5 (5.7)	.52	0.20-1.79
Preinjury antiplatelet therapy	89 (19.4)	22 (25.3)	.25	0.78-2.45
Mechanism of injury				
Fall	219 (47.8)	60 (69.0)	<.001	1.45-4.12
Tumble	97 (21.2)	10 (11.5)	.04	0.21-0.99
Car accident	108 (23.6)	10 (11.5)	.01	0.19-0.85
Others	2 (0.4)	0 (0.0)	>.99	0-28.13
Physical findings				
Heart rate, beats/min	87 ± 20	87 ± 20	.27	—2.64 to 7.93
Systolic blood pressure, mm Hg	153 ± 31.9	152 ± 26.8	.96	—6.21 to 6.59
Systolic blood pressure of <90 mm Hg	8 (1.7)	1 (1.1)	>.99	0.01-4.99
Anisocoria	22 (4.8)	9 (10.3)	.07	0.89-5.39
Bilateral fixed dilated pupils	18 (3.9)	9 (10.3)	.03	1.07-6.88
Total GCS score	14 [10-15]	14 [7-15]	.76	0-0
GCS score of 3-8	100 (21.8)	22 (25.3)	.49	0.68-2.11
Initial laboratory findings				
Platelet count, $\times 10^9$/L	18.3 [14.8-22.4]	17.0 [14.4-21.0]	.27	—2.45 to 0.50
PT-INR	1.01 [0.97-1.09]	1.40 [1.17-1.90]	<.001	0.28-0.56
APTT, s	26.6 [24.1-29.0]	30.8 [26.7-34.9]	<.001	1.6-5.9
D-dimer, μg/mL	20.7 [7.03-65.9]	5.30 [2.00-20.1]	<.001	—22.2 to —10.0
Fibrinogen, mg/mL	288 [243-350]	327 [265-405]	.01	—1.5 to 92

TABLE 1. Continued.

Variables	Control group n = 458	Preinjury anticoagulation group n = 87	*P* value[a]	95% CI[b]
Initial CT findings				
Skull cap fracture	119 (26.0)	10 (11.5)	.004	0.17-0.75
Skull base fracture	36 (7.9)	4 (4.6)	.37	0.14-1.64
Massive ASDH	274 (59.8)	53 (60.9)	.91	0.64-1.73
Massive cerebral contusion or ICH	128 (27.9)	13 (14.9)	.01	0.22-0.86
Massive AEDH	37 (8.1)	3 (3.4)	.18	0.08-1.33
Subarachnoid hemorrhage	288 (62.9)	46 (52.9)	.09	0.41-1.08
Intraventricular hemorrhage	36 (7.9)	6 (6.9)	>.99	0.29-2.17
Rotterdam CT score	3 [2-3]	3 [2-4]	.03	0-0
Basal cistern status				
Normal	370 (80.8)	57 (65.5)	.003	0.27-0.77
Compressed	52 (11.4)	18 (20.7)	.02	1.05-3.79
Absent	36 (7.9)	12 (13.8)	.096	0.85-3.89
Midline shift	94 (20.5)	31 (35.6)	.003	1.26-3.60
Treatment				
Tranexamic acid administration	231 (51.6)	33 (38.4)	.03	0.35-0.96
Anticoagulation reversal	1 (0.2)	27 (31.4)	<.001	32.56-8064
External ventricular drainage	6 (1.3)	1 (1.1)	>.99	0.02-7.36

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Decompressive craniectomy with or without hematoma removal	24 (5.2)	2 (2.3)	.41	0.05-1.77
Craniotomy and hematoma evacuation without decompressive craniectomy	29 (6.3)	13 (14.9)	.01	1.18-5.43
Burr hole hematoma evacuation	11 (2.4)	3 (3.4)	.48	0.25-5.65
Length of hospital stay, d	9 [2-23]	8.5 [3-23]	.88	—3.5 to 5
GOS score at discharge			.007	0-1
Good recovery	169 (37.2)	22 (25.6)		
Moderate disability	86 (18.9)	16 (18.6)		
Severe disability	99 (21.8)	18 (20.9)		
Vegetative state	30 (6.6)	6 (7.0)		
Dead	70 (15.4)	24 (27.9)		
mRS score at discharge			.009	0-2
0	96 (21.1)	12 (14.0)		
1	56 (12.3)	7 (8.1)		
2	63 (13.8)	10 (11.6)		
3	67 (14.7)	15 (17.4)		

TABLE 1. Continued.

Variables	Control group n = 458	Preinjury anticoagulation group n = 87	*P* value[a]	95% CI[b]
4	62 (13.6)	13 (15.1)		
5	41 (9.0)	5 (5.8)		
6	70 (15.4)	24 (27.9)		

AEDH, acute epidural hematoma; APTT, activated partial thromboplastin time; ASDH, acute subdural hematoma; CT, computed tomography; GCS, Glasgow Coma Scale; GOS, Glasgow outcome scale; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; PT-INR, prothrombin time-international normalized ratio.

Data are presented as median [IQR], mean ± SD, or n (%).

[a]*P* values and 95% CIs were calculated by the Mann-Whitney *U* test, *t* test, or Fisher test. Boldface values are statistically significant.

[b]For Mann-Whitney *U* test comparisons, the bootstrap method is used to calculate 95% CIs for median differences. before injury, including VKAs in 30 (34.5%), factor Xa inhibitors in 51 (58.6%), direct thrombin inhibitors in 5 (5.7%), and heparin infusion in 1 (1.2%). A total of 122 (22.4%) patients had a GCS score of ≤8, and 89 (16.3%) underwent emergency neurosurgery. The median length of stay was 9 days, and 17.2% of patients died during admission. Missing values were prevalent for fibrinogen and D-dimer levels (Supplemental Digital Content 3, http://links.lww. com/NEU/E534). A comparison between the preinjury anti- coagulation group (n = 87) and the control group (n = 458) showed that the preinjury anticoagulation group was older, had higher Rot- terdam CT scores, received less TXA, and underwent more emergency neurosurgery. At discharge, patients in the preinjury anticoagulation group had poorer outcomes, with lower Glasgow outcome scale scores and higher mRS scores than those in the control group. Notably, patients in the preinjury anticoagulation group had significantly lower D-dimer and higher fibrinogen levels than those in the control (Table 1).

Postinjury Time Course of Coagulation Parameters:

Graphical Analysis

Scatter plots and polynomial regression curve analysis revealed the temporal dynamics of coagulation parameters following TBI (Figure 2). In the preinjury anticoagulation group with GCS scores of ≤8, both the PT-INR and APTT peaked approximately an hour postinjury and then decreased over approximately 3 hours. The D-dimer level peaked approximately 2 hours postinjury in the severe TBI group (GCS score ≤8), irrespective of preinjury anti- coagulation. The preinjury anticoagulation group with a GCS score of <8 had a lower D-dimer level approximately 10 hours earlier than did the control group with a GCS score of ≤8. The fibrinogen levels were lower in the control group with a GCS score of ≤8 than in the other groups from the acute phase of injury and began to increase approximately 16 hours after injury. Based on the inflection points identified in these polynomial regression curves, the postinjury period was categorized into 5 periods for subsequent analysis: the first hour postinjury (T1 group, 123 patients, 123 points of time-specific blood test data), 1 to 2 hours (T2 group, 155 patients, 155 points), 2 to 6 hours (T3 group, 163 patients, 210 points), 6 to 16 hours (T4 group, 74 patients, 197 points), and 16 to 24 hours (T5 group, 30 patients, 110 points).

Associations of Preinjury Anticoagulation With Coagulation Parameters by Period: Univariate Analysis

Univariate analysis revealed that the preinjury anticoagulation group exhibited a consistently higher PT-INR and longer APTT across all periods (Figure 3, Supplemental Digital Content 4, http://links. lww.com/NEU/E535). The preinjury anticoagulation group

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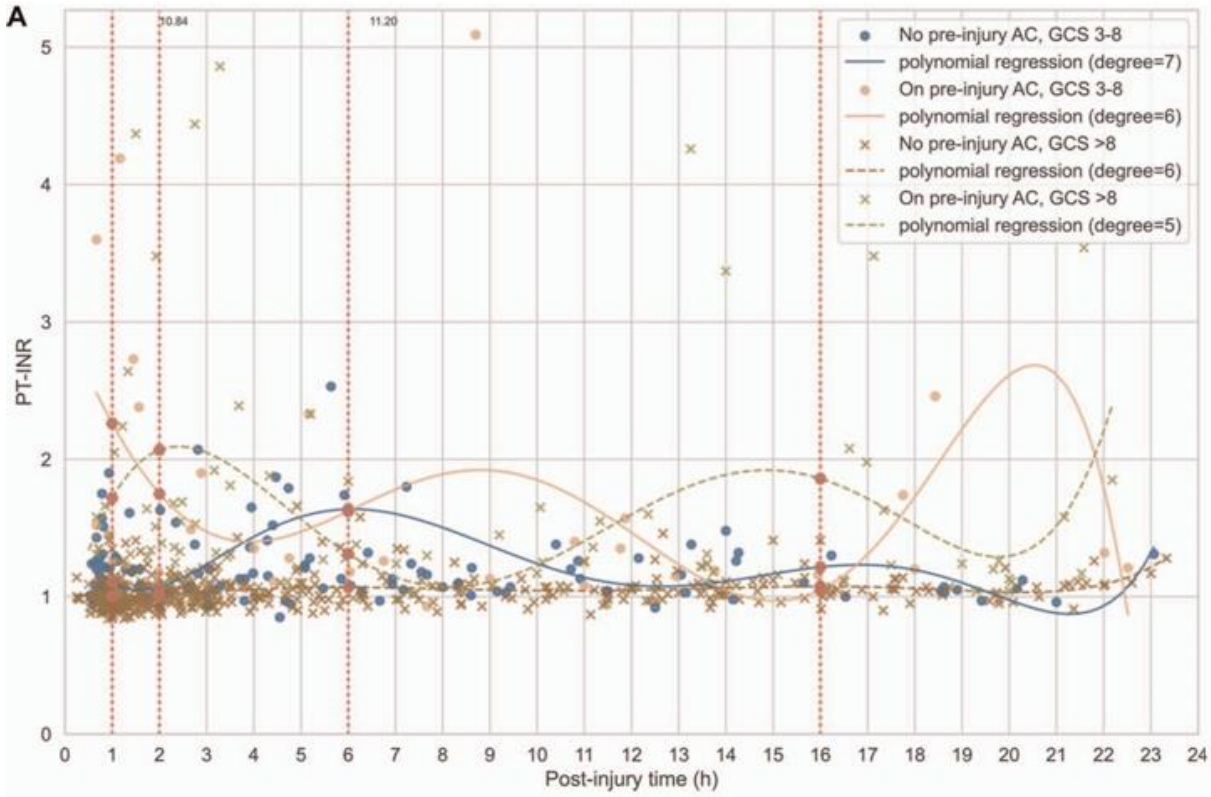
exhibited significantly lower D-dimer levels at 2 to 24 hours postinjury and significantly higher fibrinogen levels at 6 to 16 hours postinjury. The platelet count did not significantly differ between the 2 groups across any period. Therefore, ANCOVA was not conducted for the platelet count, and potential confounders were not investigated.

Association of Preinjury Anticoagulation With Coagulation Parameters by Period: ANCOVA

As the primary outcome of the study, the association between preinjury anticoagulation and coagulation parameters in various postinjury periods was analyzed by ANCOVA (Figure 3, Table 2). ANCOVA included only clinical factors significantly associated with coagulation parameters in the univariate analysis (Supplemental Digital Content 5, http://links.lww.com/NEU/E536). The AN- COVA showed significant associations of preinjury anticoagulation with D-dimer levels at 2 to 24 hours postinjury, fibrinogen levels at 6 to 16 hours postinjury, PT-INR across all periods up to 24 hours postinjury, and APTT at 1 to 16 hours postinjury. Although uni- variate analysis indicated that preinjury anticoagulation was signifi- cantly associated with prolonged APTT up to an hour postinjury, ANCOVA did not confirm this association.

Association of Clinical Factors With Coagulation Parameters by Period: ANCOVA

Among the clinical factors, the total GCS score was significantly associated with the PT-INR within 16 hours postinjury (Table 2). Massive cerebral contusion or ICH was significantly associated with the D-dimer level, especially at 2 to 6 hours and 16 to 24 hours postinjury. TXA administration was significantly as- sociated with the D-dimer level at 2 to 6 hours postinjury. No clinical factors showed a significant association with the APTT inthe first hour or with the D-dimer level up to 2 hours postinjury. Among the potential confounders, only 3 demonstrated a higher F value in ANCOVA than preinjury anticoagulation: the preinjury mRS score for fibrinogen level within 6 to 16 hours postinjury and massive cerebral contusion or ICH for the D-dimer level within 2 to 6 hours and 16 to 24 hours postinjury. The anticoagulation reversal was not significantly associated with coagulation parameters at any time.



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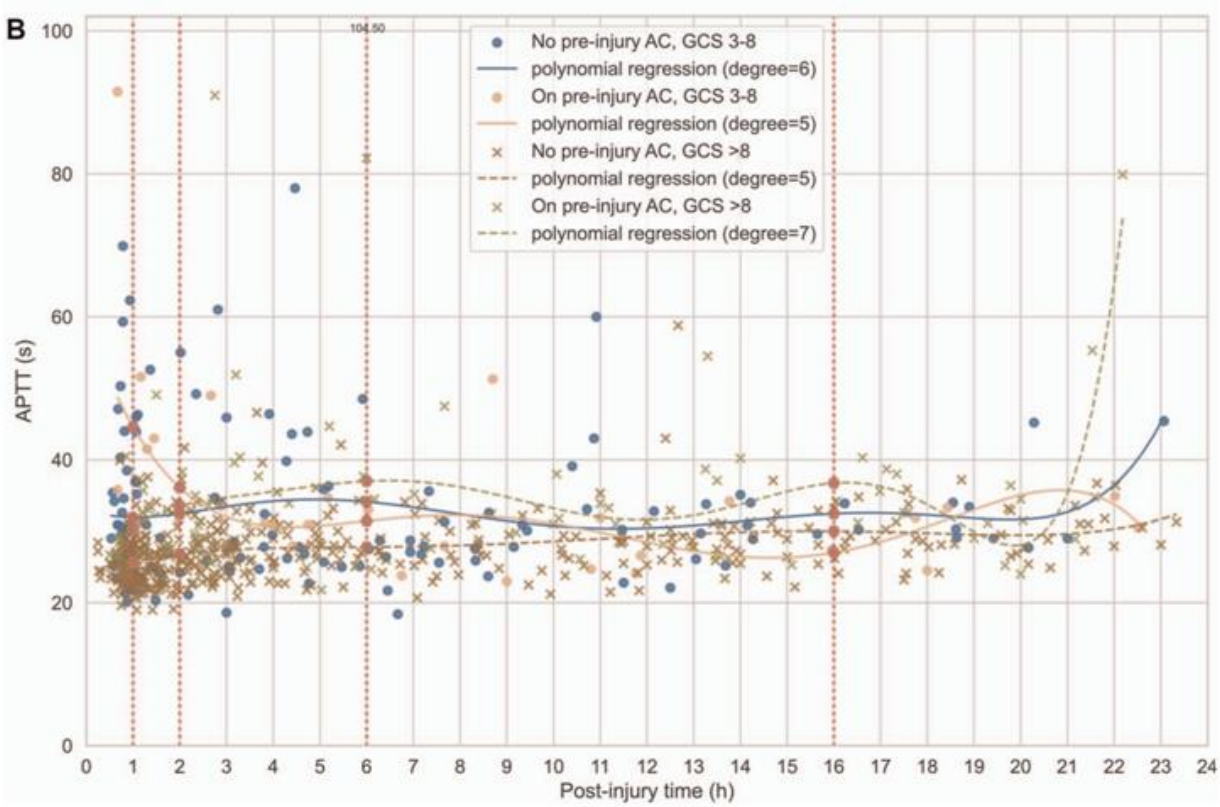
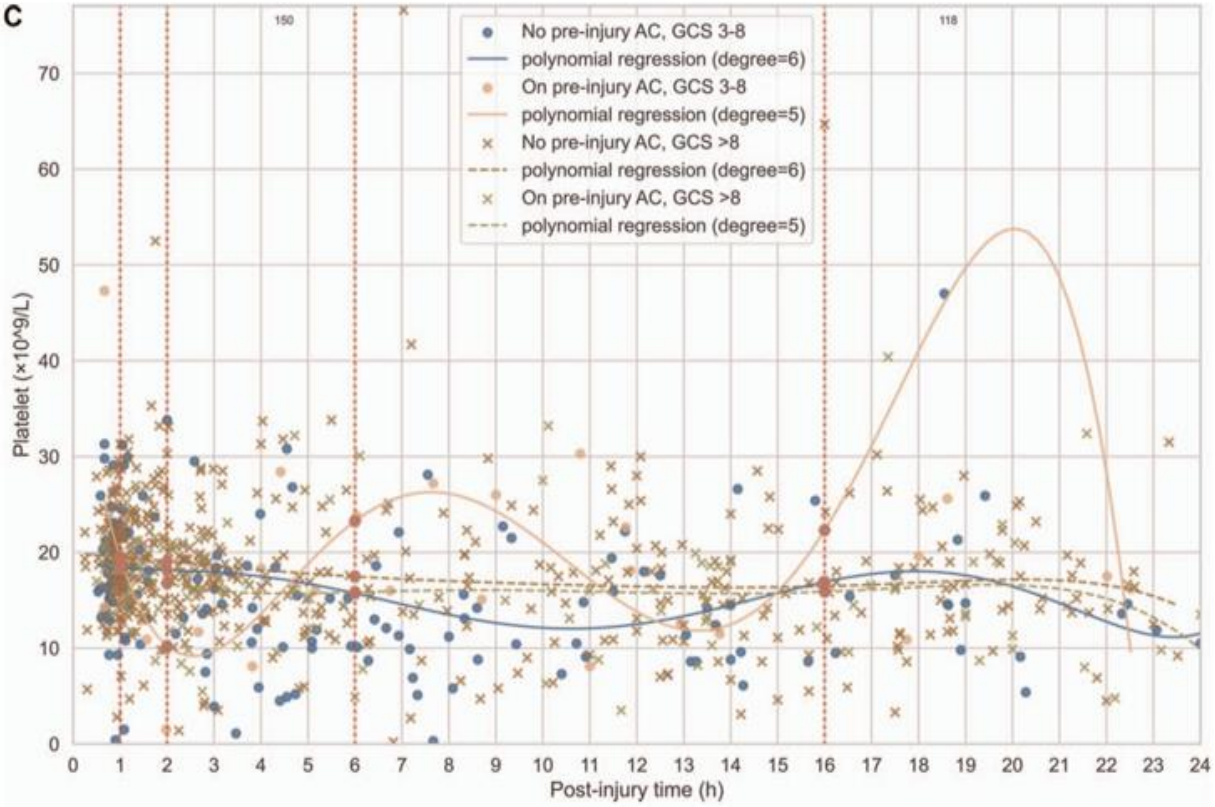


FIGURE 2. Temporal dynamics of coagulation parameters following traumatic brain injury. Scatter plots and optimized polynomial regression curves are shown for A, PT-INR, B, APTT, C platelet count, D, D-dimer, and E, fibrinogen vs time since injury. Data are categorized by preinjury anticoagulation therapy and a GCS score cutoff of 8. The polynomial degrees were determined to optimize the R2 score. The inflection points identifying the 5 periods are highlighted. AC, anticoagulation; APTT, activated partial thromboplastin time; GCS, Glasgow coma scale; PT-INR, prothrombin time-international normalized ratio.



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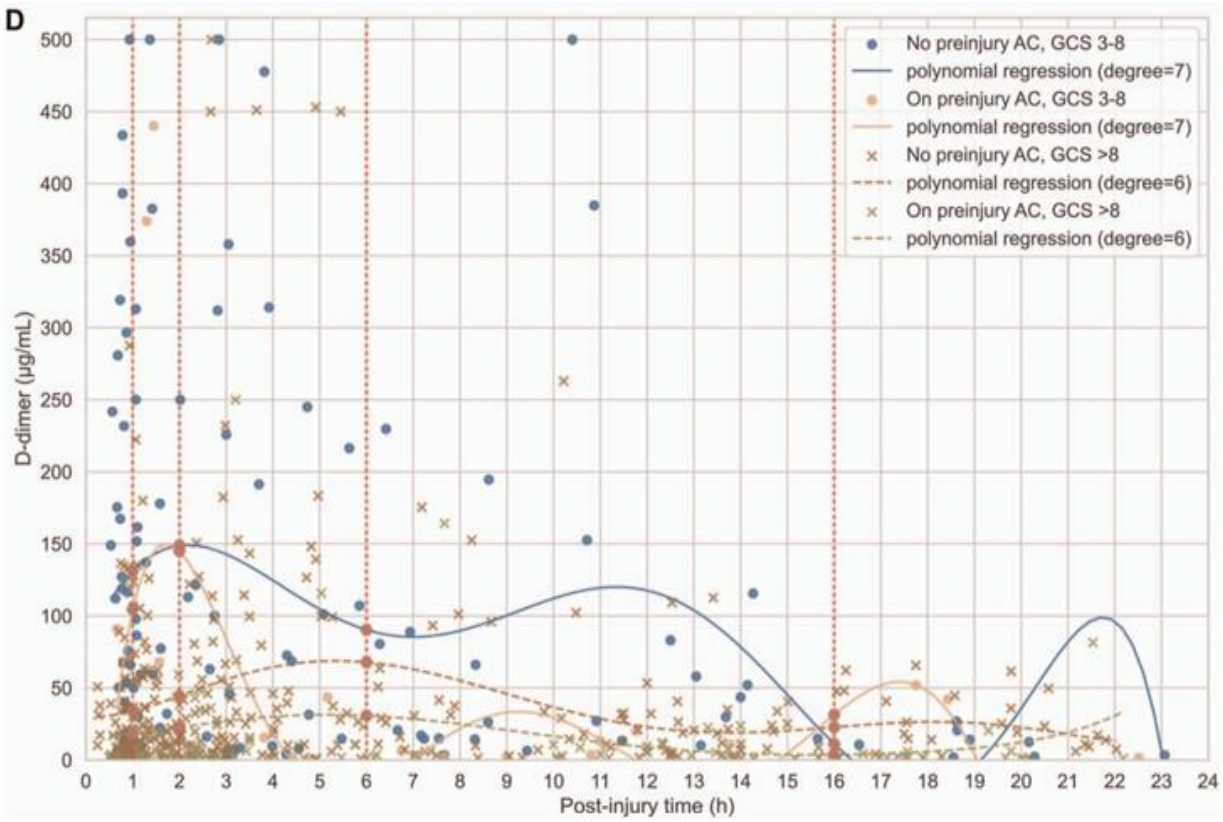

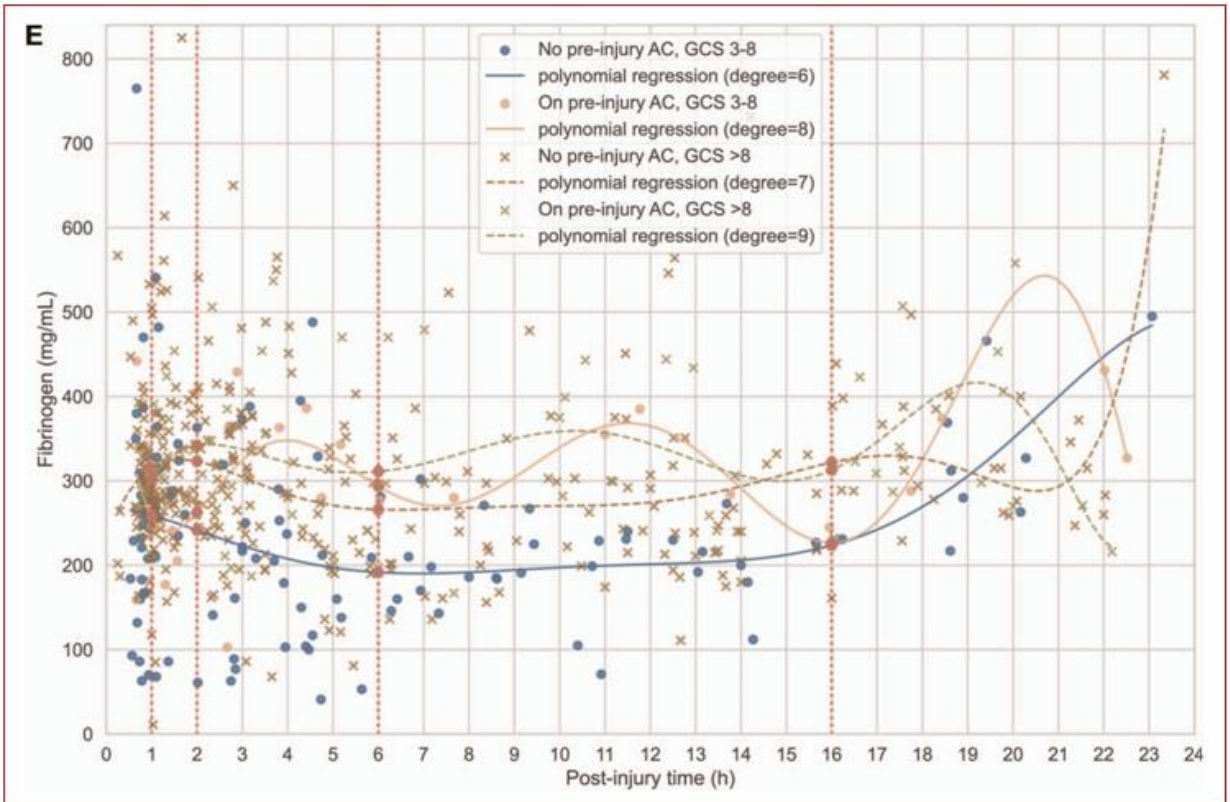

FIGURE 2. *Continued.*

Sensitivity Analyses

Supplemental Digital Content 6 shows the results of the univariate analysis. Sensitivity analysis revealed that the relationship between preinjury anticoagulation and

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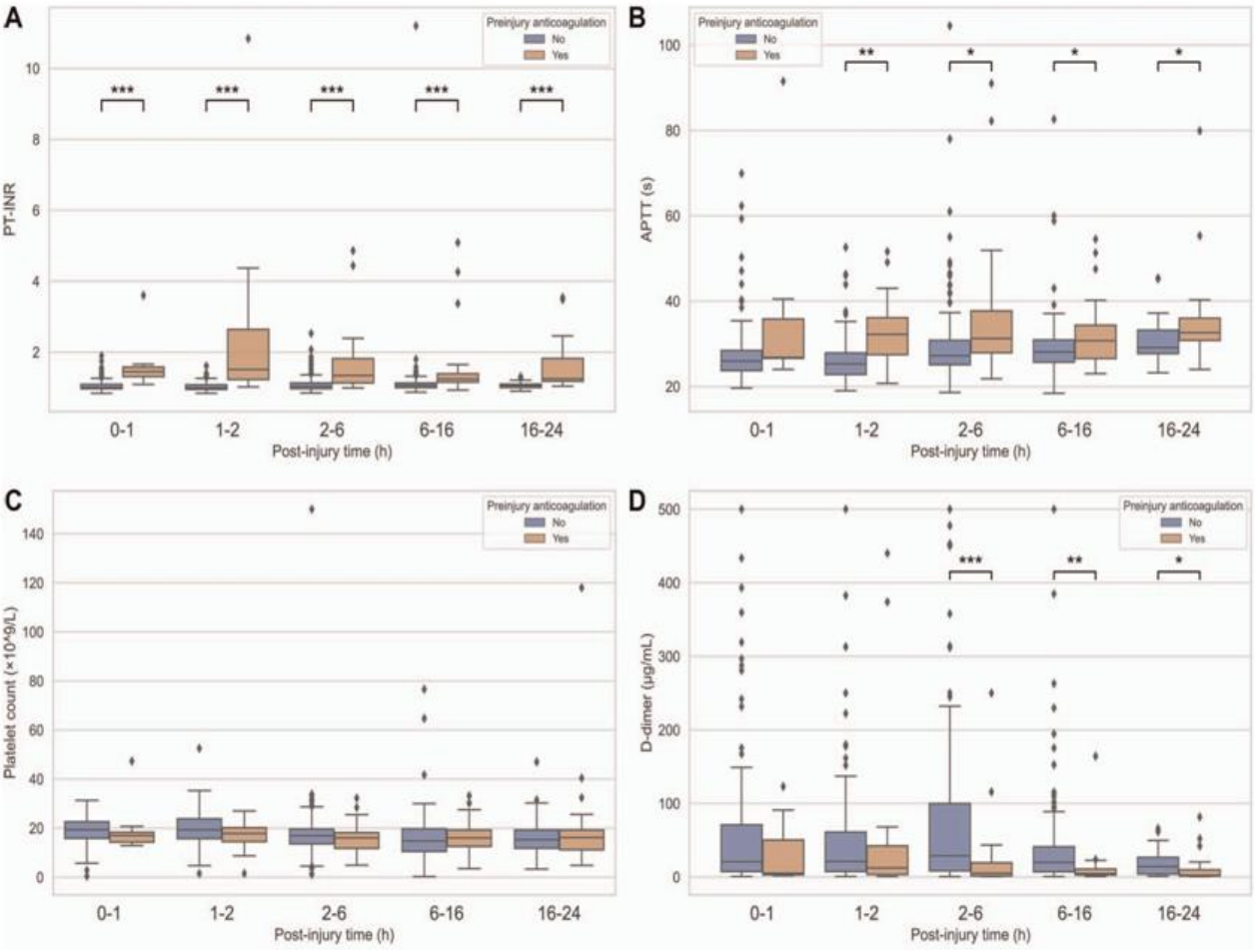
each coagulation parameter assessed by ANCOVA was consistent with the primary analysis, except for fibrinogen (Supplemental Digital Content 7, The significant association between fibrinogen levels and preinjury anticoagulation indicated by the primary ANCOVA was no longer significant when outliers were excluded in the sensitivity analysis. In addition, some changes were observed in the potential confounders.

DISCUSSION

This study revealed several significant findings regarding the impact of preinjury anticoagulation on TBI-induced coagulopathy. First, despite more severe TBI signs and poorer outcomes, the preinjury anticoagulation group had significantly lower D-dimer levels. Second, the preinjury anticoagulation group exhibited significantly lower D-dimer levels at 2 to 24 hours postinjury, sug gesting that the D-dimer level may not reliably represent TBI severity, especially during this period. Third, preinjury anti- coagulation was consistently associated with an elevated PT-INR for up to 24 hours and a prolonged APTT within 1 to 24 hourspostinjury. These findings suggest that preinjury anticoagulation may cause hemorrhagic progression and delayed traumatic ICH, primarily through its effect of PT and APTT prolongation.

An elevated D-dimer level is reportedly associated with poor TBI outcomes.[8,13] Therefore, our finding that the preinjury anti- coagulation group with poorer outcomes had lower D-dimer levels than the controls is inconsistent with previous reports. The D-dimer elevation following TBI is primarily attributed to the following mechanisms. First, the tissue factor (TF) is released from cerebral vessels into the bloodstream through direct vascular injury or defragmentation from microvascular failure during TBI.[14,15] This triggers the extrinsic coagulation cascade, leading to thrombin production and subsequent amplification of the procoagulant response, finally resulting in consumptive coagulopathy.[16] Increased thrombin then indirectly elevates the D-dimer level by enhancing fibrin production. Anticoagulants reduce fibrin production and, subsequently, the D-dimer level by inhibiting thrombin activity.



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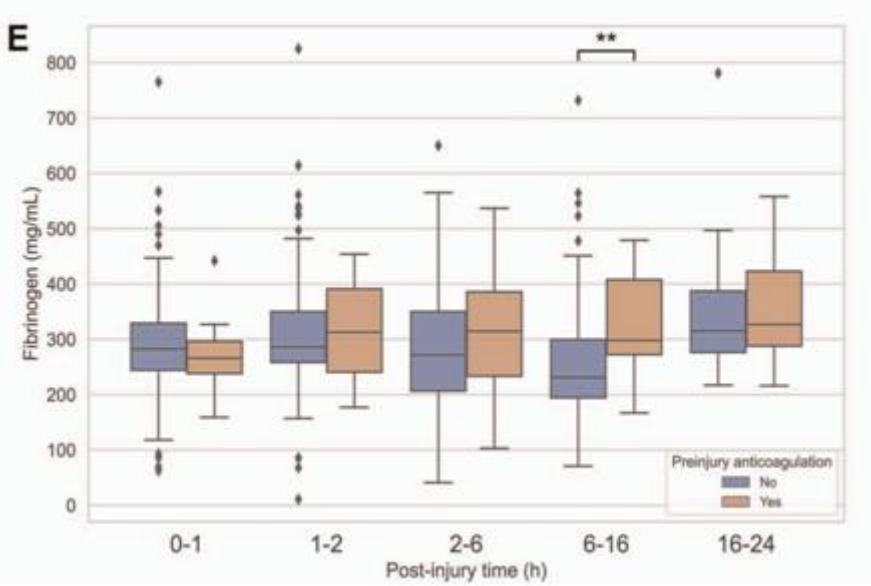

FIGURE 3. ***Comparison of coagulation parameters between the 2 groups according to the postinjury period. Boxplots of* A,** ***PT-INR,* B,** ***APTT,* C,** ***platelet count,* D,** ***D-dimer, and* E,** ***fibrinogen are shown by the postinjury period in the 2 groups with and without preinjury anticoagulation therapy. *P < .05, **P < .01, ***P < .001 (calculated by analysis of covariance). APTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio.***

This pharmacological effect on the synthesis of large amounts of TBI-derived thrombin may have resulted in the lower D-dimer levels observed in the preinjury anticoagulation group. However, because preinjury anticoagulation should not affect the release of TF, a direct marker of brain tissue injury, whether preinjury anticoagulation reduces or only masks TBI-induced hyper- fibrinolysis remains unclear. A detailed assessment of fibrinogen levels could help clarify this issue. However, our primary and sensitivity analyses showed contradictory results regarding the as- sociation between preinjury anticoagulation and fibrinogen variability. These discrepancies may be due to the large number of missing fibrinogen values, which were heavily influenced by outliers, and the lack of statistical power. Therefore, this study did not determine the effect of preinjury anticoagulation on fibrinogen levels. Additional methods, such as thromboelastography, might help to further elucidate the underlying mechanism.

TABLE 2. Results of Analysis of Covariance for Association Between Clinical Factors and Coagulation Parameters by Postinjury Period

Associated factors	Coagulation parameters with significant associations in each postinjury period[a]				
	0-1 h	1-2 h	2-6 h	6-16 h	16-24 h
Preinjury anticoagulation	APTT (*P* = .001, F = 10.6)	APTT (*P* = .02, F = 6.01)		APTT (*P* = .01, F = 6.75)	APTT (*P* = .01)[c]
	PT-INR (*P* < .001, F = 29.0)	PT-INR (*P* < .001, F = 57.0)	PT-INR (*P* < .001, F = 39.6)	PT-INR (*P* < .001, F = 24.1)	PT-INR (*P* < .001, F = 32.8)
	imer (*P* < .001, = 16.4)			D-dimer (*P* = .002, F = 10.5)	D-dimer (*P* = .03,F F = 4.78)
	Fibrinogen (*P* = .005,F = 8.19)				
Potential confounders[b]					
Glasgow coma scale score	APTT (*P* = .03, F = 4.90)				
	PT-INR (*P* = .02,	PT-INR (*P* = .01, F = 6.74)		PT-INR (*P* = .047, F = 4.01)	F = 5.92)
	Fibrinogen (*P* = .02,F = 5.51)				
Bilateral fixed dilated pupils	APTT (*P* = .03,F = 4.64)				
	PT-INR (*P* < .001,			PT-INR (*P* = .001, F = 10.7)	F = 12.8)
Rotterdam CT score	PT-INR (*P* = .04, F = 4.26)				
	D-dimer (*P* = .02, F = 5.59)				
Massive cerebral contusion or ICH	D-dimer (*P* < .001,				D-dimer (*P* = .03,
F = 21.7)					F = 5.06)
Systolic blood pressure	APTT (*P* = .02, F = 6.01)				
	PT-INR (*P* < .001, PT-INR (*P* < .001, F = 15.5)				F = 12.2)
Skull base fractures	D-dimer (*P* = .002, F = 9.79)				

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	TXA administration	D-dimer ($P < .001$, F = 14.0)
Preinjury mRS score		Fibrinogen ($P = .003$, F = 9.42)
Age	APTT ($P = .009$,F = 7.00)	
	PT-INR ($P = .03$, F = 4.60)	PT-INR ($P = .002$, F = 10.0)

ANCOVA, analysis of covariance; APTT, activated partial thromboplastin time; CT, computed tomography; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; PT-INR, prothrombin time-international normalized ratio; TXA, tranexamic acid.

[a]For each coagulation parameter in each time period, the largest F value is indicated in bold. ANCOVA was conducted only for those time periods for which a previous *t* test showed

a significant association between preinjury anticoagulation and coagulation parameters. ANCOVA was not conducted for platelets because the previous univariate analysis showed no significant association with coagulation parameters.

[b]Only those potential confounders that showed a significant association with coagulation parameters by univariate regression analysis or a *t* test were used as confounding factors

in ANCOVA. Anticoagulation reversal is not presented because they were not significantly associated with coagulation parameters in any time periods.

[c]ANCOVA was not conducted because no confounders were significantly associated with APTT in the previous univariate analysis. Instead, the *P*-value calculated by univariate regression analysis is presented.

The preinjury anticoagulation group exhibited significantly lower D-dimer levels at 2 to 24 hours postinjury, suggesting that the D-dimer level may not reliably represent TBI severity, es- pecially during this period. TXA administration, more common in the control group, may affect D-dimer levels. A previous study showed that early TXA administration significantly reduces D-dimer levels at 3 hours postinjury.[17] In our study's ANCOVA, TXA administration was significantly associated with D-dimer levels at 2 to 6 hours but did not counteract the effect of preinjury anticoagulation. Previous studies have not fully investigated the impact of preinjury anticoagulation on timed coagulation alter- ations after TBI.[18] In our study, patients with severe TBI ex- hibited peak D-dimer levels at approximately 2 hours postinjury, regardless of preinjury anticoagulant use, suggesting that preinjury anticoagulation does not entirely suppress TBI-induced coagul- opathy. By contrast, our graphical analysis showed a faster de- crease in postpeak D-dimer levels in the preinjury anticoagulationgroup. This implies that hyperfibrinolysis peaks at an intensity that exceeds pharmacological effects until approximately 2 hours postinjury, while anticoagulants have a stronger effect thereafter. This characteristic trend corresponds with the momentum of thrombin production, meaning that the progression of TBI- induced coagulopathy peaks at approximately 2 hours post- injury. Further studies are needed to confirm this, especially considering the timing of the last dose of anticoagulants and the degree of efficacy in patients taking VKAs. Previous studies have shown that the D-dimer level peaks at 3 to 6 hours postinjury depending on injury severity, similar to our results.[8,18,19] However, reports on the specific timing of D-dimer decline vary.[8,18,20] Our graphical analysis showed a decrease in D-dimer levels starting approximately 16 hours postinjury in the control group with GCS scores of ≤8 and from 4 to 6 hours in the preinjury anticoagulation group with GCS scores of ≤8. Notably, our focus on graphical analysis differs from previous studies that analyzed D-dimer levels in the same patient at multiple predefined time points.

Preinjury anticoagulation was consistently associated with PT-INR elevation up to 24 hours postinjury and APTT prolongation within 1 to 24 hours postinjury. Although a previous study in- dicated a similar association between preinjury anticoagulation and the PT-INR or APTT post-TBI, the time course after injury was not addressed, partly because fewer patients received anti- coagulation therapy than in our study.[6] VKAs are known to prolong the PT, and some DOACs have also been reported to prolong the PT in a concentration-dependent manner, although not consis-tently.[21,22] Consequently, the increased PT-INR in the preinjury anticoagulation group might mainly represent the pharmacological effects of anticoagulants. However, the prolonged APTT observed in the preinjury anticoagulation group may be attributed not only to anticoagulant pharmacology but also to prolonged TBI-induced coagulopathy. The primary mechanism of post-TBI PT and APTT prolongation involves TF release into the systemic circulation, which causes a consumptive increase in thrombin production, prolonging PT and APTT.[18] Simultaneously, TF shortens PT and APTT by activating factor VII and then factor X.[23] VKAs and factor Xa inhibitors inhibit factor X activation in this process, which may explain the more prolonged PT and APTT in the preinjury anticoagulation group. However, unlike DOACs, VKAs inhibit not only factor X but also factors II, VII, and IX and act indirectly. Therefore, further analysis should distinguish between VKAs and DOACs. Overall, our findings suggest that coagulopathy, mani- festing as PT and APTT prolongation, may play an essential role in increasing postinjury bleeding in TBI patients on anticoagulants. Given the importance of anticoagulant pharmacology in this process, prompt anticoagulation reversal is critical for mitigating increased bleeding risk and preventing delayed intracerebral hemorrhage. However, because of their limited use, we could not determine whether anticoagulant reversal agents affect the pro- gression and persistence of TBI-induced coagulopathy. Anti-coagulation was reversed in 83% of patients receiving VKAs but only 18% of those receiving DOACs, which is attributed to theunavailability of Xa inhibitor reversal

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agents in Japan during the study period. Consequently, the association of anticoagulation reversal with TBI-induced coagulopathy, particularly in DOAC users, was not adequately investigated in this study. Future research with more data focused on anticoagulation reversal is warranted to clarify the appropriate reversal strategy and timing.

Limitations

Our study has several limitations. First, the prospective registry of only elderly Japanese patients was analyzed retrospectively. Because only initial CT findings were collected, the associations between preinjury anticoagulation and hemorrhagic progression or delayed ICH were not examined, highlighting the need for further research. Although polynomial regression is considered useful even when data are not collected at predetermined time points,[24] our graphical analysis requires further validation because of the retrospective nature of the data. Second, although morepatients used DOACs in this study than in a recent large study,[6] neither the overall number nor the proportion of DOAC users was substantial. Thus, a subanalysis distinguishing between VKAs and DOACs was not possible. The influence of the different phar-macological mechanisms of VKAs and DOACs on TBI-induced coagulopathy warrants further investigation. However, both agents share the common pharmacological effect of inhibiting thrombin generation, likely leading to similar inhibition of D-dimer generation. The major difference between VKAs and DOACs is that VKAs have unpredictable pharmacokinetics. To address this, the sensitivity analysis excluded cases with outliers in coagulation parameters, including PT-INR. The results were largely consistent with the primary analysis. Third, because of thelarge number of missing values, the statistical power was insufficient, especially for fibrinogen, a potential indicator of coagulopathy severity.[25]

CONCLUSION

Despite more severe TBI signs and poorer outcomes, the preinjury anticoagulation group had significantly lower D-dimer levels. This finding suggests that the D-dimer level may not reliably represent TBI severity, especially within 2 to 24 hours postinjury. Preinjury anti- coagulation was also associated with an elevated PT-INR up to24 hours and a prolonged APTT within 1 to 24 hours postinjury. These changes might have been caused not only by the pharmacological effects of anticoagulants but also by their impact on the mechanism of TBI-induced coagulopathy. Prospective studies to validate our findings are warranted.

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