Activity of factor VII in patients with isolated blunt traumatic brain injury: Association with coagulopathy and progressive hemorrhagic injury

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BACKGROUND: Given the importance of factor VII (FVII) in extrinsic pathway of coagulation cascade, we sought to elucidate the relationship between FVII and traumatic brain injury–induced coagulopathy and progressive hemorrhagic injury (PHI).

METHODS: Eighty-one patients with isolated traumatic brain injury, 16 years or older, were recruited between 2010 and 2012. Blood was collected on arrival in the emergency department and analyzed with activated partial thromboplastin time, international normalized ratio, platelet count, and activity of FVII. Coagulopathy was defined as thrombocytopenia (platelet count < 120,000/mL) or elevated international normalized ratio of greater than 1.2 or prolonged activated partial thromboplastin time greater than 40 seconds at admission. PHI was present when the follow-up computed tomographic scan reported any increase in size or number of the hemorrhagic lesions. Logistic regression examined the risks for coagulopathy and PHI.

RESULTS: Mean (SD) FVII activity in patients with coagulopathy was 85.69% (34.88%), which was significantly lower than patients without coagulopathy (99.57% [29.37%], p = 0.04). Isolated traumatic brain injury patients with FVII activity less than 77.5% have an odds ratio for coagulopathy of 5.52 (95% confidence interval, 1.82–16.68; p = 0.03) relative to patients with FVII activity of 77.5% or greater. Mean (SD) FVII activity in patients with PHI was 70.76% (18.21%), which was significantly lower than patients without PHI (105.76% [32.27%], p = 0.001). A stepwise logistic regression analysis identified FVII less than 77.5% (odds ratio, 4.53; 95% confidence interval, 1.62–12.67; p = 0.004) as a predisposing risk factor independently associated with the presence of PHI. The overall mortality rate in the study population was 7.4% (n = 6). The plasma FVII in death patients (91.44% [47.19%]) was slightly lower than that in survival patients (92.01% [32.04%]). However, there was no statistical difference between the two groups (p = 0.95).

CONCLUSION: A decrease of FVII activity significantly contributes to the coagulopathy and PHI in patients with isolated traumatic brain injury. (J Trauma Acute Care Surg. 2014;76:114–120. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: Factor VII; isolated traumatic brain injury; coagulopathy; progressive hemorrhagic injury.

Traumatic brain injury (TBI) remains the leading cause of death and long-term disability after trauma. At least one fifth of patients with severe TBI (sTBI) die of their injuries, making TBI the number one cause of death in people younger than 45 years.1 Acute coagulopathy in the absence of extracranial injuries is a severe complication of TBI and may contribute to secondary injury and mortality. A recent meta-analysis showed an overall prevalence of TBI-associated coagulopathy of 32.7% (range, 10–97.3%).2 The presence of coagulation disorder has been linked to the procession of hemorrhagic lesions and is associated with increases in morbidity and mortality.2–4 The mechanism underlying coagulopathy following TBI is still poorly understood. The most commonly accepted hypothesis of the pathogenesis of coagulopathy following TBI implies alterations in local and systemic coagulation and fibrinolytic pathways secondary to the release of tissue factor (TF). Coagulation factor VII (FVII) is the first enzyme involved in the extrinsic pathway and has a key role in TF-initiated coagulation cascade. In the presence of cerebral TF released from damaged brain, inactive FVII is converted by limited proteolysis to its fully activated two-chain form, VIIa. After activation, VIIa rapidly converts coagulation factor IX and coagulation factor X into their active forms, thus initiating the generation of thrombin and fibrin clot formation. Release of brain TF after brain injury results in an overwhelming activation of the extrinsic coagulation pathway, leading to consumptive insufficiency of coagulation factors, such as FVII. Administration of rFVIIa can reduce growth of hematoma in intracerebral hemorrhage and reverse coagulopathy in sTBI,5–7 which suggests that FVII activity in plasma may determine the coagulation status and progression of hemorrhage after TBI.

Unfortunately, few studies have investigated the activity of FVII and the relationship between FVII and coagulopathy in isolated TBI patients. However, some studies have investigated the activity of FVII in plasma with functional consequences of...
coagulation response in cerebral bleeding disorders, which showed that an increased risk for primary intracranial hemorrhage is associated with low activity of FVII.\(^8\) Those studies may shed light on the relationship between FVII activity and the occurrence of coagulopathy and progression of hemorrhage following TBI. Therefore, the aim of the present study was to investigate the changes of plasma FVII activity in isolated TBI and whether the activity of FVII in plasma is associated with the risk for coagulopathy and progression of hemorrhage after TBI.

PATIENTS AND METHODS

Study Design

This was a prospective, single-center, observational study. The study was conducted between August 2010 and December 2012 at Shanghai Neurotrauma Center in Huashan Hospital. The University Hospital Medical Ethics Board approved the research protocol. Patients were eligible for study inclusion in case of TBI and an emergency department (ED) admission Glasgow Coma Scale (GCS) score less than 13. For the present study, a selection was made of patients with isolated TBI, defined as computed tomographic (CT) scan–confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an extracranial Abbreviated Injury Scale (AIS) score less than 3. Exclusion criteria were an extracranial AIS score greater than 3, younger than 16 years, use of anticoagulant (clopidogrel, aspirin, and coumarin, et al.), liver failure, or missing coagulation parameters upon ED admission. Written informed consent was obtained from the patient or a legal representative. Baseline demographic and clinical history was recorded using standardized data collection forms. Demographic and injury variables included age, sex, head AIS score, extracranial AIS score, placement of an intracranial pressure (ICP) catheter, and GCS score at ED admission. TBI severity was categorized as moderate (GCS score, 9–13) or severe (GCS score, 3–8).

Definition of Progressive Hemorrhagic Injury

Only patients with two or more head CT scans in the first 72 hours were included. The CT scans were interpreted by two independent neuroradiologists, and hemorrhagic progression was determined by evaluating their reports. Progressive hemorrhagic injury (PHI) was present when the follow-up CT scan reported any increase in size or number of the hemorrhagic lesions, including newly developed ones.\(^9\)

Measurement of FVII Activity

Blood samples were collected on admittance to the hospital. Samples of venous blood for FVII assay were drawn into Vacutainer tubes containing 3.8% sodium citrate (9:1, vol/vol). Plasma was separated by centrifugation for 20 minutes at 2,000 G and stored at −80°C for later analysis. FVIIa was assayed as previously described, with a kit using a soluble recombiant truncated TF that is selectively deficient in promoting FVII activation but retains FVIIa cofactor function, thus allowing quantitative plasma FVIIa assessment (Staclot VIIa-rTF, Diagnostica Stago, Asnières-sur-Seine, France). Values were expressed as percentage of the standard, which is 100% by definition. The normal range of FVIIa is 55% to 150%. The within-run and between-run coefficients of variation were 7.8% and 6.4%, respectively.

Coagulation Parameters

For this study, we registered lactate in millimole per liter, blood pH, hemoglobin (Hb) in millimole per liter, activated partial thromboplastin time (aPTT), the international normalized ratio (INR), and platelet count upon ED admission. Coagulopathy was defined as an aPTT greater than 40 seconds and/or INR greater than 1.2 and/or a platelet count less than 120 × 10⁹/L.\(^5,10\)

Statistical Analysis

Data were summarized using means and SDs or medians and interquartile ranges (IQRs) for continuous variables, depending on the distribution of the data and percentages for discrete variables. Continuous variables were evaluated with the Student’s t test. \(\chi^2\) test or two-sided Fisher’s exact test was used for categorical variables. For identifying the risk factors for the development of coagulopathy and PHI and mortality, a stepwise logistic regression analysis was performed. Risk factors with \(p < 0.2\) from the bivariate analysis were included in the model. All statistical analyses were performed using IBM SPSS Statistics 17.0 (IBM, New York, NY). For all analyses, \(p < 0.05\) was considered statistically significant.

RESULTS

Clinical Characteristics of Patients With Isolated TBI

From August 2010 through December 2012, 81 patients met inclusion criteria for the study. The total database consisted of 272 patients, of which 81 subjects were eligible for inclusion for data analysis. Reasons for exclusion were an extracranial AIS score greater than 3 (n = 87), younger than 16 years (n = 9), use of anticoagulant (n = 16), penetrating injury (n = 6), missing FVII parameters within 48 hours after admission (n = 64), and miscellaneous reasons (n = 9). Males constituted 80.2% of the population, and the overall mean (SD) age was 49.49 (15.24) years. The demographic and clinical characteristics of the study population were summarized in Table 1. The most common intracranial pathologies in order of descending frequency included intraparenchymal hematoma (69.1%), subdural hemorrhage (53.1%), subarachnoid hemorrhage (48.1%), and epidural hematoma (21%). In this population, 54.3% (n = 44) had coagulopathy. In 79.5% (n = 35) of the coagulopathic patients, the diagnosis included thrombocytopenia, followed by elevated INR in 40.9% (n = 18) and elevated aPTT in 9.1% (n = 4).

FVII Activity Correlated With INR, But Not aPTT, and Platelet Amount

Correlations were sought between FVII activity with INR, aPTT, and platelet amount. FVII activity correlated inversely with INR \((r = −0.67, p < 0.001)\). As shown in Figure 1, the FVII activity did not correlate with the aPTT and platelet amount. To examine the interaction between FVII activity and
coagulopathic risk, the study population was dichotomized according to the calculated threshold level of 77.5% for FVII activity as the INR is equal to 1.2.

Patients with low FVII activity had significantly higher INR (1.22 [0.13] vs. 1.04 [0.09]; p < 0.001), higher aPTT (33.70 [7.54] vs. 25.49 [4.48]; p < 0.001), lower fibrinogen (FIB) (2.63 [1.91] vs. 2.76 [1.91]; p = 0.14), and higher lactate (3.78 [5.94] vs. 2.76 [1.91]; p = 0.63) compared with patients with normal INR. Moreover, FVII activity did not correlate with FIB (93.63% [33.35%] for FIB > 1 mg/L vs. 99.37% [29.37%] for FIB ≤ 1 mg/L; p = 0.88), aPTT (93.47% [36.00%] for aPTT > 15 s vs. 99.37% [29.37%] for aPTT ≤ 15 s; p = 0.48), or platelet count (92.85% [32.27%] for platelet > 100,000/µL vs. 99.37% [29.37%] for platelet ≤ 100,000/µL; p = 0.71). Further investigation showed that FVII activity had no relationship with the severity of injury (93.47% [36.00%] for GCS score of 3–8 vs. 87.56 [22.52] for GCS score of 9–12; p = 0.48), AIS (92.85% [32.27%] for AIS score ≤ 5 vs. 90.69% [34.88%] for AIS score > 5; p = 0.04). We then investigated the relationship of FVII activity with other potential variations. FVII activity was significantly lower in patients with prolonged INR (62.31% [15.04%]; p < 0.001), aPTT (62.63% [11.80%]; p = 0.02), and higher lactate (76.84% [25.99%] for lactate > 2.2 mmol/L; p < 0.001) compared with those with normal INR (100.41% [31.87%]), aPTT (93.46% [33.07%]), and lactate (105.96% [32.87%] for lactate ≤ 2.2 mmol/L). However, there was no statistically significant difference between patients with low and normal platelet (91.46% [31.32%] in low platelet vs. 92.57% [35.54%] in normal platelet; p = 0.88). Moreover, FVII activity did not correlate with Craniotomy (62.31% [15.04%] for Craniotomy vs. 87.56 [22.52] for no Craniotomy; p = 0.48).

Bivariate analysis was performed to identify risk factors for FVII activity lower than 77.5%, which showed that only lactate greater than 2.2 mmol/L (odds ratio [OR], 10.71; 95% confidence interval [CI], 3.62–31.68; p < 0.001) was associated with a significantly higher risk, whereas sex, age, head AIS score, GCS score, Hb, pH, and ICP were not (Fig. 2).

**FVII Activity and Coagulopathy**

Overall, 54.3% (n = 44) of the study population presented with coagulopathy after isolated TBI. Mean (SD) FVII activity in patients with coagulopathy was 85.69% (34.88%), which was significantly lower than that of patients without coagulopathy (99.37% [29.37%], p = 0.04). We then investigated the relationship of FVII activity with other potential variations. FVII activity was significantly lower in patients with prolonged INR (62.31% [15.04%]; p < 0.001), aPTT (62.63% [11.80%]; p = 0.02), and higher lactate (76.84% [25.99%] for lactate > 2.2 mmol/L; p < 0.001) compared with those with normal INR (100.41% [31.87%]), aPTT (93.46% [33.07%]), and lactate (105.96% [32.87%] for lactate ≤ 2.2 mmol/L). However, there was no statistically significant difference between patients with low and normal platelet (91.46% [31.32%] in low platelet vs. 92.57% [35.54%] in normal platelet; p = 0.88). Moreover, FVII activity did not correlate with FIB (82.20% [30.36%] for FIB ≤ 1 g/L vs. 93.63% [33.35%] for FIB > 1 g/L; p = 0.27), aPTT (94.10% [23.16%] for aPTT ≤ 1 mg/L vs. 91.08% [36.32%] for aPTT > 1 mg/L; p = 0.71). Further investigation showed that FVII activity had no relationship with the severity of injury (93.47% [36.00%] for GCS score of 3–8 vs. 87.56 [22.52] for GCS score of 9–12; p = 0.48), AIS (92.85% [32.27%] for AIS score ≤ 5 vs. 90.69% [34.44%] for AIS score > 5; p = 0.77), and increase of ICP (92.09% [27.39%] for ICP ≤ 15 mm Hg vs. 100.34% [37.40%] for ICP > 15 mm Hg; p = 0.29). Bivariate analysis was performed to identify risk factors for coagulopathy, which showed that head AIS score of 5, GCS score of 8 or less, FVII less than 77.5%, and d-dimer greater than 1 mg/L was associated with a significantly higher risk.

![Figure 1](image_url)

**Figure 1.** Analysis of correlation between FVII activity with INR, aPTT, and platelet amount in TBI patients. To determine the correlation between FVII activity and INR, aPTT or platelet amount, respectively, the values for FVII activity of each patient were plotted against the corresponding INR (A), aPTT (B), or platelet amount (C).

**Table 1.** Demographic and Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>81</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>65 (80.2)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>49.49 (15.24)</td>
</tr>
<tr>
<td>Head AIS score, median (IQR)</td>
<td>4 (3.5–5)</td>
</tr>
<tr>
<td>GCS score, mean (SD)</td>
<td>6.89 (2.79)</td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>1.11 (0.14)</td>
</tr>
<tr>
<td>aPTT, mean (SD), s</td>
<td>28.63 (7.06)</td>
</tr>
<tr>
<td>Platelet, mean (SD), ×10⁹/L</td>
<td>137.44 (56.7)</td>
</tr>
<tr>
<td>FVII, mean (SD), %</td>
<td>91.94 (33.0)</td>
</tr>
<tr>
<td>d-dimer, mean (SD), mg/L</td>
<td>3.78 (5.94)</td>
</tr>
<tr>
<td>FIB, mean (SD), g/L</td>
<td>2.63 (1.81)</td>
</tr>
<tr>
<td>Lactate, mean (SD), mmol/L</td>
<td>112.48 (27.98)</td>
</tr>
<tr>
<td>Hb, mean (SD), g/L</td>
<td>130.36 (16.1)</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>7.46 (0.77)</td>
</tr>
<tr>
<td>pH, mean (SD)</td>
<td>24 (29.6)</td>
</tr>
<tr>
<td>Surgery in 72 h, n (%)</td>
<td>12 (14.8)</td>
</tr>
<tr>
<td>Only ICP monitor</td>
<td>24 (30.6)</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>45 (55.6)</td>
</tr>
<tr>
<td>Subtype of hemorrhage,* n (%)</td>
<td>39 (48.1)</td>
</tr>
<tr>
<td>Subdural</td>
<td>17 (21.0)</td>
</tr>
<tr>
<td>Epidural</td>
<td>43 (53.1)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>56 (69.1)</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>12 (14.8)</td>
</tr>
</tbody>
</table>

*Some patients fall into multiple categories.

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TABLE 2. Clinical Characteristics Among Isolated TBI Patients With Low FVII Activity or High FVII Activity

<table>
<thead>
<tr>
<th></th>
<th>FVII Activity &lt; 77.5% (n = 31)</th>
<th>FVII activity ≥ 77.5% (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>47.42 (17.66)</td>
<td>50.78 (13.56)</td>
<td>0.34</td>
</tr>
<tr>
<td>Head AIS score, median (IQR)</td>
<td>4 (4–5)</td>
<td>4 (3–5)</td>
<td>0.66</td>
</tr>
<tr>
<td>GCS score, mean (SD)</td>
<td>6.77 (2.97)</td>
<td>6.96 (2.70)</td>
<td>0.77</td>
</tr>
<tr>
<td>Specific laboratory test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>1.22 (0.13)</td>
<td>1.04 (0.09)</td>
<td>0.001</td>
</tr>
<tr>
<td>aPTT, mean (SD), s</td>
<td>33.70 (7.55)</td>
<td>25.48 (4.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet, mean (SD), ×10^12/L</td>
<td>125.74 (51.71)</td>
<td>144.70 (58.92)</td>
<td>0.15</td>
</tr>
<tr>
<td>FVIIIC, mean (SD), %</td>
<td>61.17 (11.18)</td>
<td>111.02 (27.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>d-dimer, mean (SD), mg/L</td>
<td>4.53 (6.76)</td>
<td>3.30 (5.39)</td>
<td>0.37</td>
</tr>
<tr>
<td>FIB, mean (SD), g/L</td>
<td>2.07 (1.29)</td>
<td>2.98 (2.00)</td>
<td>0.026</td>
</tr>
<tr>
<td>Lactate, mean (SD), mmol/L</td>
<td>3.93 (2.58)</td>
<td>1.97 (0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb, mean (SD), g/L</td>
<td>114.19 (31.80)</td>
<td>111.42 (25.61)</td>
<td>0.67</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>128.10 (15.78)</td>
<td>131.76 (16.29)</td>
<td>0.32</td>
</tr>
<tr>
<td>pH, mean (SD)</td>
<td>7.48 (0.06)</td>
<td>7.45 (0.08)</td>
<td>0.051</td>
</tr>
<tr>
<td>ICP, mean (SD), mm Hg</td>
<td>18.77 (10.50)</td>
<td>17.47 (8.36)</td>
<td>0.58</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>3 (10.0)</td>
<td>3 (6.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hospital stay, mean (SD), d</td>
<td>24.13 (23.38)</td>
<td>20.46 (13.24)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

whereas sex, age, FIB, lactate, Hb, and ICP were not (Fig. 3). Stepwise logistic regression analysis identified the following independent risk factors for the development of coagulopathy: head AIS score of 5 (OR, 3.25; 95% CI, 1.97–9.09; p = 0.024), GCS score of 8 or less (OR, 4.03; 95% CI, 1.21–13.46; p = 0.02), and FVII activity less than 77.5% (OR, 5.51; 95% CI, 1.82–16.68; p = 0.003).

Although coagulopathic patients experienced higher ICP (19.69 [8.74] vs. 16.0 [9.04]), higher mortality (9.1% vs. 5.4%), and longer stay (23.0 [20.92] vs. 20.51 [13.23]) compared with their noncoagulopathic counterparts, there was no significant difference between the coagulopathic and noncoagulopathic groups.

FVII Activity and PHI

In this population, PHI occurred in 32 (39.5%) of 81 patients. FVII activity in patients with PHI was 70.76% (18.21%), which was significantly lower than that of patients without PHI (105.76% [32.27%], p < 0.001). Intracerebral hemorrhage progressed in 52.3% (23 of 44) of the coagulopathic patients but in only 24.3% (9 of 37) of those without coagulopathy (p = 0.001). Bivariate analysis was performed to identify risk factors for the presence of PHI, which showed that coagulopathy and FVII less than 77.5% were associated with a significantly higher risk, whereas sex, age, head AIS score, GCS score, FIB, d-dimer, lactate, Hb, pH, and ICP were not (Fig. 4). A stepwise logistic regression analysis identified FVII less than 77.5% (OR, 4.53; 95% CI, 1.62–12.67; p = 0.03) and coagulopathy (OR, 2.17; 95% CI, 1.19–6.15; p = 0.004) as a predisposing risk factors independently associated with the presence of PHI.

FVII Activity and Mortality

The overall mortality rate in the study population was 7.4% (n = 6). Among six death patients, one patient died of uncontrollable intracranial infection, three patients died of severe sepsis, two patients died of uncontrollable ICP. Activity of FVII in fatalities (91.44% [47.19%]) was relatively lower than that in survival patients (92.01% [32.04%]). However, there was no statistical difference between the two groups (p = 0.95).

**DISCUSSION**

This is the first study reporting the activity of FVII in a cohort of patients with sTBI. In this study, our findings show that FVII activity correlates with INR but not with aPTT and platelet amount in sTBI patients. FVII activity in patients with coagulopathy or PHI is significantly lower than that of patients without coagulopathy or PHI.

The pathophysioligic mechanism underlying coagulopathy in isolated TBI is multifactorial and still a subject of debate. It is thought that isolated TBI induces massive TF release into the general circulation, which results in the overwhelming activation of the extrinsic coagulation pathway, leading to consumptive coagulopathy and bleeding disorders.2 Soluble TF concentration is equally low in all TBI patients and unrelated to routine coagulation tests, which suggests that soluble TF may not play a significant role in TBI-associated coagulopathy. Our results show that the activity of FVII in plasma among coagulopathic patients is significantly lower than those without coagulopathic counterparts, and a decrease of FVII activity is an independent risk for coagulopathy after isolated TBI. This suggests that the FVII activity in plasma may play an important role in TBI-induced coagulopathy.

Up to date, only two studies have investigated the alteration of coagulation factor, including FVII, in patients with trauma-induced coagulopathy. Both of them demonstrated that FVII activity decreased in patients with coagulopathy after trauma. Those studies focused on the general trauma patients, not on isolated TBI patients only. Shaz et al. demonstrated that the lower factor activities including FVII were more likely
secondary to increased hemodilution than coagulation factor depletion because lower hematocrit resulting from hemodilution was significantly correlated with lower factor activities especially in FVII. In our study, the hematocrit between low FVII activity patients and high FVII activity counterparts is not significantly different, which excludes the effect of hemodilution on the activity of coagulation factors. In addition, our study shows that the isolated TBI patients with coagulopathy has lower GCS score and higher head AIS score than those of the counterparts without coagulopathy. This result is similar to the results of previous studies noting a positive correlation between coagulation abnormalities and the severity of brain injury. However, these findings differ from the findings of Shaz et al., where coagulation values did not correlate with GCS score, head AIS score, and positive head CT finding. The disparity of the results may be caused by the population of the study by Shaz et al., which included 91 traumatic patients, not isolated TBI patients only. Moreover, the patients in the study of Shaz et al. had a head AIS score of 1 (2) and GCS score of 13 (4), while the patients in our study had a median head AIS of 4 (1), and GCS of 6.89 (2.79). Thus, injury severity of head may result in differences seen in coagulation factor levels and their correlation with brain injury between these studies.

Jansen et al. have postulated that reduced coagulation factor activity is associated with hypoperfusion in severely injured trauma patients. Supporting data demonstrate that the activity of coagulation factors II, V, VII, IX, X, and XI, correlate negatively with base deficit, a marker of tissue hypoperfusion. In our study, decrease of FVII activity is associated with higher lactate, another marker of hypoperfusion, which supports the hypothesis that tissue hypoperfusion results in the reduction of FVII activity. However, a recent study shows that 60.4% of the coagulopathic patients do not experience base deficit level greater than 6 mmol/L at admission to the hospital, which challenges the relationship between hypoperfusion and early coagulopathy after isolated TBI and suggests that coagulopathy does not occur exclusively in conjunction with hypoperfusion in patients of sTBI. The heterogeneity of tests used, definitions of coagulopathy, severity of TBI, and diversity of study population among the studies may explain such dissimilar results. Therefore, the underlying mechanism of a decrease of FVII activity in coagulopathic patients with sTBI should be clarified in the further exploration.

PHI is a strong predictor of mortality, and thus recognizing and addressing the factors associated with its progression may have an impact on mortality and disability from TBI. Several factors have been implicated as determinants of PHI, including male sex, low initial level of consciousness, older age, volume of the initial hematoma, and coagulopathy. In clinical practice, the association between laboratory tests and PHI is still complex and controversial. We find that FVII activities in patients with PHI (70.78% [18.21%]) is significantly lower than those of patients without PHI (105.76% [33.27%]). Further investigation shows that besides coagulopathy, FVII activity less than 77.5% is an independent risk for PHI. This finding suggests that FVII activities may play a significant role in TBI-induced PHI but does not exclude the possibility that other coagulation factors may contribute to PHI.

We notice that most of patients with TBI has normal range FVII activity (55–150% of activity). FVII activity

| Male | 2.35 (0.76-7.23) |
| Age<55 | 0.72 (0.30-1.73) |
| Head AIS<5 | 3.24 (1.27-8.27) |
| GCS>8 | 3.22 (1.13-9.16) |
| FVII<77.5% | 5.14 (1.87-14.18) |
| D-D dimers>1mg/L | 3.07 (1.12-8.41) |
| FIB<1g/L | 1.83 (0.51-6.66) |
| Lac>2.2mmol/L | 1.44 (0.60-3.46) |
| Hb<90g/L | 2.68 (0.86-8.42) |
| ICP>15mmHg | 2.10 (0.82-5.51) |

**Figure 3.** Risk for isolated TBI-associated coagulopathy.

**Figure 4.** Risk factors of PHI in patients with isolated TBI.
correlates inversely with INR, and the cutoff value for FVII activity is 77.5% as a threshold for relative FVII insufficiency in TBI patients. Logistic regression analysis identified FVII less than 77.5% as a predisposing risk factors independently associated with the presence of coagulopathy and PHI. In clinical practice, recombinant FVIIa has been used to correct the coagulopathy in patients with TBI. Although it is shown that rFVIIa can correct coagulopathy timely and reduce the expanse of hematoma after TBI, rFVIIa has potential risk for thromboembolic complications. INR is not a reliable test for the presence of coagulopathy, not an indicative parameter of amounts of clotting factors, and not useful in guiding treatment, particularly when mildly or moderately abnormal. Therefore, plasma FVII activities could be used as an indication for administering rFVIIa.

There are several limitations to the present examination, the most important being the retrospective analysis of prospectively collected data. Second, we used a threshold level of 77.5% for FVII activity to dichotomize the patients as the INR is equal to 1.2. Although FVII levels correlates inversely with INR, the correlation coefficient ($r = -0.67$) suggests that the correlation between INR and FVII activity was moderate, thus making it possible that the calculated threshold of FVII activity may misidentify the coagulopathic patients in this study. Third, because of the retrospective nature of the current analysis, we are unable to know the baseline activity of FVII before the event; it is virtually impossible to evaluate the actual alteration of FVII activity after sTBI, introducing a possible source of bias. Finally, we have not comprehensively assessed the levels of coagulation factors in TBI patients. Therefore, FVII activity could not solely contribute to TBI-induced coagulopathy and PHI in our study.

In conclusion, to the best of our knowledge, this is the first study investigating the role of FVII in coagulopathy and PHI in patients sustaining sTBI. The decrease of FVII activity significantly contributes to the coagulopathy and PHI in patients with sTBI.

AUTHORSHIP
All authors helped to draft the manuscript or critically revised it. All coauthors agree about the content of the article and have read the manuscript and approved its submission to the Journal of Trauma and Acute Care Surgery. Furthermore, X.W. participated in the design, coordination, and data acquisition of the study. B.P. and X.L. participated in the data acquisition, database management, and statistical analysis. J.H. and L.Z. participated in the design of the study. J.Y. and Z.D. participated in the data acquisition. M.Y. conceived the study, participated in the design of the study, and finalized the manuscript.

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DISCLOSURE
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