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ORIGINAL WORK

Extended Coagulation Profiling in Isolated Traumatic Brain Injury: A CENTER-TBI Analysis

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Abstract

Background: Trauma-induced coagulopathy in traumatic brain injury (TBI) remains associated with high rates of complications, unfavorable outcomes, and mortality. The underlying mechanisms are largely unknown. Embedded in the prospective multinational Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, coagulation profiles beyond standard conventional coagulation assays were assessed in patients with isolated TBI within the very early hours of injury.

Methods: Results from blood samples (citrate/EDTA) obtained on hospital admission were matched with clinical and routine laboratory data of patients with TBI captured in the CENTER-TBI central database. To minimize confounding factors, patients with strictly isolated TBI (iTBI) ($n=88$) were selected and stratified for coagulopathy by routine international normalized ratio (INR): (1) INR < 1.2 and (2) INR ≥ 1.2. An INR > 1.2 has been well adopted over time as a threshold to define trauma-related coagulopathy in general trauma populations. The following parameters were evaluated: quick's value, activated partial thromboplastin time, fibrinogen, thrombin time, antithrombin, coagulation factor activity of factors V, VIII, IX, and XIII, protein C and S, plasminogen, D-dimer, fibrinolysis-regulating parameters (thrombin activatable fibrinolysis inhibitor, plasminogen activator inhibitor 1, antiplasmin), thrombin generation, and fibrin monomers.

Results: Patients with iTBI with INR ≥ 1.2 ($n=16$) had a high incidence of progressive intracranial hemorrhage associated with increased mortality and unfavorable outcome compared with patients with INR < 1.2 ($n=72$). Activity of coagulation factors V, VIII, IX, and XIII dropped on average by 15–20% between the groups whereas protein C and S levels dropped by 20%. With an elevated INR, thrombin generation decreased, as reflected by lower peak height and endogenous thrombin potential (ETP), whereas the amount of fibrin monomers increased. Plasminogen activity significantly decreased from 89% in patients with INR < 1.2 to 76% in patients with INR ≥ 1.2. Moreover, D-dimer levels significantly increased from a mean of 943 mg/L in patients with INR < 1.2 to 1,301 mg/L in patients with INR ≥ 1.2.

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Conclusions: This more in-depth analysis beyond routine conventional coagulation assays suggests a counterbalanced regulation of coagulation and fibrinolysis in patients with iTBI with hemostatic abnormalities. We observed distinct patterns involving key pathways of the highly complex and dynamic coagulation system that offer windows of opportunity for further research. Whether the changes observed on factor levels may be relevant and explain the worse outcome or the more severe brain injuries by themselves remains speculative.

Keywords: CENTER-TBI, Coagulopathy, Fibrin monomers, Progressive intracranial hemorrhage, Thrombin generation, Traumatic brain injury

Introduction

Traumatic brain injury (TBI) remains a significant medical and socioeconomic burden for patients, relatives, and health care systems [1]. Current calculations estimate approximately 69 million cases of TBI to occur each year around the globe [2]. Apart from the initial injury, posttraumatic courses, including outcomes, may be complicated by preexisting hemostatic derangements or derangements that develop with TBI [3]. Recent observational data from the prospective multicentered Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study have confirmed the presence of laboratory coagulopathy based on conventional coagulation assays (CCAs) in approximately 20% of all patients with isolated TBI (iTBI) on hospital admission [4]. Independent risk factors may include not only the degree of impact, shock, hypothermia, and hypotension but also preinjury use of anticoagulant and/or antiplatelet therapies [4]. Patients with preinjury anticoagulant and/or antiplatelet therapy were twice as likely to have an abnormal coagulation profile as those without premedication, and this was associated with greater expansion of hemorrhagic lesions and a higher risk of delayed traumatic intracranial hemorrhage [4, 5].

Apart from the physical impact, which typically leads to disruptions of the cerebral vasculature and the blood–brain barrier, along with hemorrhage, TBI-associated factors may further alter the overall hemostatic state, leading to disruptions in the balance between hypocoagulability and hypercoagulability, thereby exacerbating the initial injury [6]. The current definitions of post-TBI coagulopathy remain heterogeneous and are often based on CCAs, such as prothrombin time with its surrogates, prothrombin ratio and international normalized ratio (INR), and activated partial thromboplastin time (aPTT). In addition, the precise mechanisms that relate to the different phenotypes of coagulopathy seen with TBI are still incompletely understood. The aim of the present study was to further characterize alterations within the coagulation system of patients with iTBI by assessing concentration changes of selected proteins indicative for hypercoagulation and hypocoagulation beyond CCAs within the early hours of injury. In this context, further interest was given to the assessment of hemorrhagic injuries, expansion, and outcome in the presence of hemostatic abnormalities after iTBI.

Methods

Patients and Blood Sampling

The present study was embedded into the longitudinal observational CENTER-TBI study, which had recruited patients from 60 selected centers across Europe and Israel between December 2014 and December 2017 [7]. The study was conducted in accordance with local ethical regulations and with all relevant laws of the European Union and the country of the recruiting site, including relevant laws and regulations on the use of human materials. Informed consent by the patients and/or the legal representative/next of kin was obtained according to the local legislations.

Patient inclusion criteria were clinical diagnosis of TBI, indication for computed tomography (CT) scanning, presentation to a study center within 24 h of injury, and informed consent according to local and national requirements [7]. Patients were excluded if they had any severe preexisting neurological disorder that could have confounded the outcome assessments.

Of the 60 recruiting CENTER-TBI study sites across Europe, the following centers had collected and submitted blood samples for the present analysis: (1) Antwerp University Hospital (Belgium), (2) University of Cambridge (UK), (3) Helsingin Yliopisto Finnish Institute for Molecular Medicine (Finland), (4) University Hospitals Leuven (Belgium), (5) Karolinska University Hospital Stockholm (Sweden), (6) University Hospital of Aachen (Germany), (7) Kaunas University of Technology (Lithuania), (8) Leids Universitair Medisch Centrum (Netherlands), and (9) Turku University Central Hospital (Finland). On site, EDTA and citrated blood tubes were centrifuged at $1.500 \times g$ for 10 min. Platelet poor plasma samples were aliquoted and frozen at − 80 °C directly or at − 20 °C for a maximum of 48 h before being transferred to the storage temperature of − 80 °C. Samples were sent

from the local recruiting sites to the central CENTER-TBI laboratory at the University of Pécs (Hungary) first and then sent on dry ice to the receiving Institute for Research in Operative Medicine (IFOM) in Cologne, Germany, for further analysis.

Sample Selection

On receipt, the samples were linked to the clinical and laboratory data comprehensively collected into the CENTER-TBI central database (INCF Neurobot 2.0; INCF, Stockholm, Sweden). To exclude any confounding effects by external factors (e.g., extracranial injuries and/or relevant interim anticoagulant or procoagulant therapies), further sample analysis was restricted to samples received from patients with iTBI (AIS_{Brain} 2–5) only and to those with available data on coagulation captured in the CENTER-TBI central database for the first 4 h after injury. Samples received from patients with documented preexisting neurological disorders, preinjury anticoagulant and/or antiplatelet therapy, presence of extracranial injuries ($AIS_{Extracranial} > 0$), and missing critical data points were excluded a priori. For further analysis, the first documented blood sample collected after local hospital admission was considered together with the clinical and laboratory data captured on the same timeline. The INR on admission captured in the CENTER-TBI central database served to distinguish two groups of samples and patients: those with (1) INR < 1.2 and those with (2) INR ≥ 1.2. An INR > 1.2 has been well adopted over time as a threshold to define trauma-related coagulopathy in general trauma populations [8].

Clinical Data

The prospectively recorded clinical and laboratory data points in the scope of the CENTER-TBI study for patient characterization and captured in the CENTER-TBI central database included demographics, injury characteristics, medical presentation on admission (Glasgow Coma Scale score, systolic blood pressure, heart rate, temperature), scheduled emergency surgical intervention, neuroworsening, parameters for tissue injury and hypoperfusion (base excess and shock index), hemodilution (platelets, hemoglobin, and hematocrit), and outcome (death and Glasgow Outcome Score Extended [GOS-E]). Presence of progressive intracranial hemorrhage (PIH) was defined by the incidence of extradural or subdural hematoma or subarachnoid hemorrhage on the initial CT scan and increase in hemorrhage size/volume on the follow-up CT scan. Follow-up data on functional outcome, including mortality and GOS-E, were obtained 6 months post injury. A GOS-E between 1 and 4 (dead, vegetative state, low-severity disability, and high-severity disability) was considered unfavorable.

Extended Coagulation Testing

CCAs to evaluate the coagulation status at the time point of blood sampling were performed by the Institute of Transfusion Medicine (ITM) at the Cologne-Merheim Medical Center, Cologne (Germany), and included the following: Quick's value, INR, aPTT, thrombin time, fibrinogen, and antithrombin. The assessments beyond CCAs included coagulation factor V, VIII, IX, and XIII antigens; protein C; protein S; D-dimer; and plasminogen. Citrated plasma samples were analyzed by using HemosIL assays (Werfen, Bedford, MA) on the ACL TOP CTS 700 device (Werfen).

Enzyme-Linked Immunosorbent Assay

Soluble plasminogen activator inhibitor 1 (PAI-1) as a marker for fibrinolysis regulation was quantified via the commercial Human Serpin E1/PAI-1 DuoSet ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's recommendations.

Thrombin Generation and Fibrinolysis-Regulating Markers

Thrombin generation, thrombin activatable fibrinolysis inhibitor (TAFI), antiplasmin, and fibrin monomers were assessed at the Ludwig Boltzmann Institute (Vienna, Austria). By using a quantitative fluorogenic assay (STG-BleedScreen; Stago, Asnières-sur-Seine, France) on the thrombin generation analyzer (ST Genesia; Stago), the thrombin generation parameters (1) peak height and (2) endogenous thrombin potential (ETP) were determined. TAFI and the fibrinolysis regulator antiplasmin were quantified by a colorimetric assay using the STA-Stachrom TAFI and STA-Stachrom Antiplasmin kits (Stago). The level of fibrin monomers was measured with an immunoturbidimetric technology by using the STA-Liatest FM kit (Stago). For these assays, the frozen citrated plasma samples were thawed at 37 °C for 10 min in a water bath and stored at room temperature for up to 1 h.

Statistical Analysis

For the descriptive data analysis, metric data are presented as medians with interquartile ranges and categorical data are presented as percentages. Statistical differences in patient characteristics and coagulation factors/parameters were tested by using the Mann–Whitney U-test and χ^2 test, respectively. A p value < 0.05 was considered statistically significant. Statistical analyses were performed by using SPSS statistics version 25 for Windows (IBM Corp., Armonk, NY) and GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA).

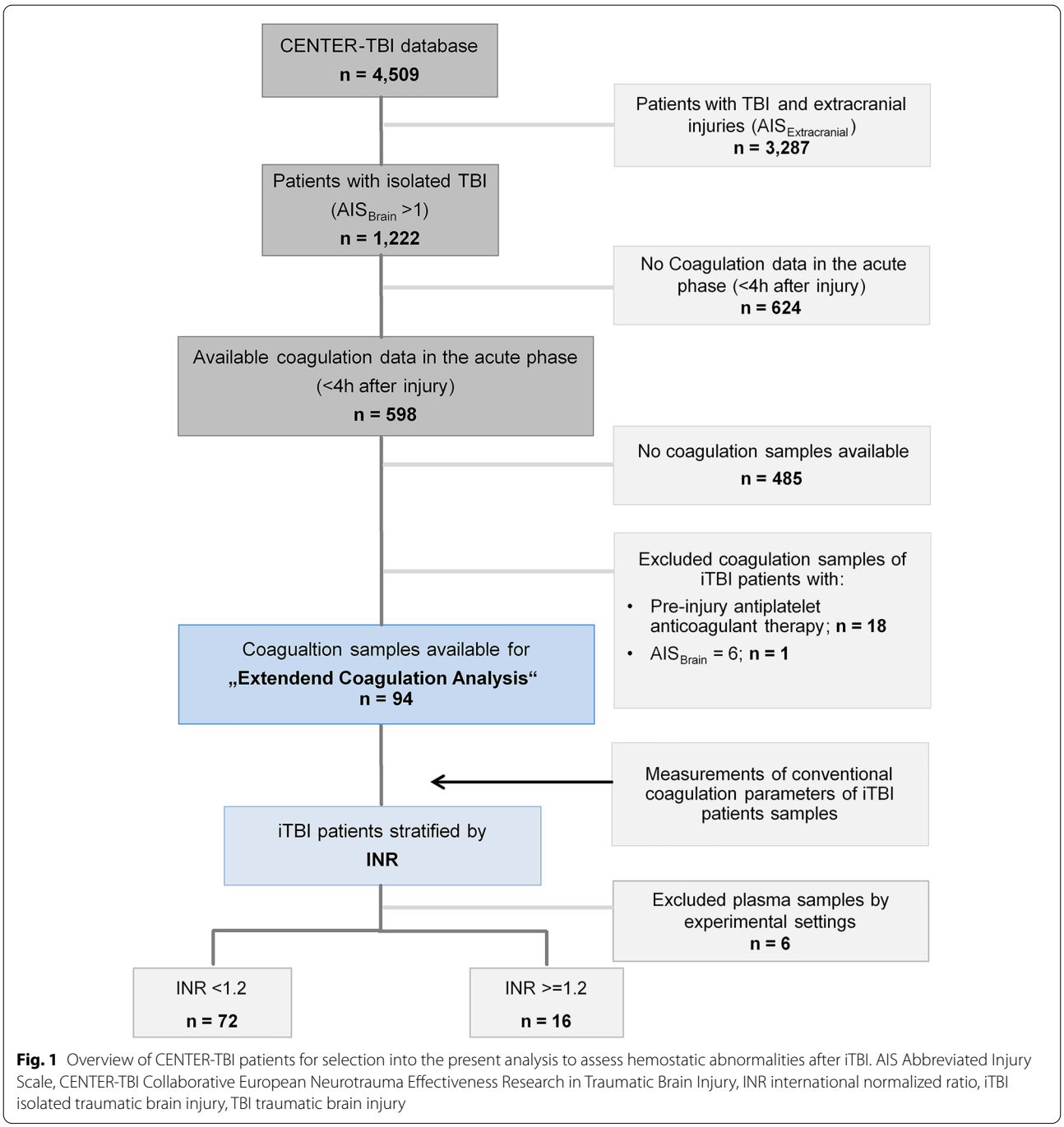

Fig. 1 Overview of CENTER-TBI patients for selection into the present analysis to assess hemostatic abnormalities after iTBI. AIS Abbreviated Injury Scale, CENTER-TBI Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury, INR international normalized ratio, iTBI isolated traumatic brain injury, TBI traumatic brain injury

Results

Study Cohort Characteristics

Overall, 4,509 patients were included in the CENTER-TBI core study database; of these, 3,287 had to be excluded for coexisting extracranial injuries and 624 for missing data (Fig. 1). Of the 598 patients with iTBI who had available coagulation data within the acute phase after TBI (< 4 h after injury), blood samples of 485 patients were missing, and to minimize interference and interfering factors, an additional 19 patients were excluded from the analysis (Fig. 1). Due to quality loss of samples during shipment and experimental settings, blood samples of another six patients had to be excluded.

Table 1 Characteristics of patients with iTBI stratified by INR ($n = 88$)

	INR <1.2 ($n = 72$)	INR ≥1.2 ($n = 16$)
Demographics		
Age, median (IQR) (years)	41.0 (30 to 57)	27.0 (22 to 54)
Age ≥ 75, n (%)	5 (6.9)	NA
Male sex, n (%)	48 (66.6)	12 (75)
Injury characteristics, n (%)		
Blunt TBI	65 (90.3)	15 (93.8)
AIS 2	6 (8.3)	1 (6.3)
AIS 3	27 (37.5)	1 (6.3)
AIS 4	21 (29.2)	6 (37.5)
AIS 5	18 (25)	8 (50)
Injuries identified on initial CT scan, n (%)		
Diffuse axonal injury	9 (12.5)	2 (12.5)
Extradural hematoma	15 (20.8)	4 (25)
Subdural hematoma	28 (38.8)	7 (43.7)
Subarachnoid hemorrhage	34 (47.2)	8 (50)
Midline shift	12 (16.7)	6 (37.5)*
Basal cistern compression	6 (8.3)	2 (12.5)
Depressed skull fracture	7 (9.7)	3 (18.8)
Severe contusion	2 (2.7)	2 (12.5)
Medical presentation at admission (ED)		
GCS, median (IQR)	14.0 (10.0 to 15.0)	12.0 (7.5 to 15.0)
SBP, median (IQR) (mm Hg)	134.0 (123 to 150)	135.5 (113 to 163)
Heart rate, median (IQR) (bpm)	84.0 (75 to 97)	82.0 (68 to 90)
Temperature, median (IQR) (°C)	36.4 (35.8 to 36.9)	36.0 (35.6 to 36.4)
Scheduled for emergency surgical intervention, n (%)	11 (15.3)	2 (12.5)
Neuroworsening, n (%)	8 (11.1)	3 (18.8)
Parameter for tissue injury and hypoperfusion, median (IQR)		
Base excess (mmol/L)	−1.1 (−2.9 to 0.55)	−2.7 (−3.7 to −0.9)
Shock index	0.61 (0.52 to 0.71)	0.64 (0.48 to 0.73)
Parameter for hemodilution, median (IQR)		
Platelet count (per nL)	220.5 (181.5 to 273.5)	211.5 (177.8 to 235.3)
Hemoglobin (g/dL)	13.9 (12.8 to 14.5)	13.4 (12.1 to 14.4)
Hematocrit	41.0 (38.0 to 44.0)	44.0 (37.7 to 45.7)*
ED therapy, n (%)		
Blood products (e.g., RBC, FFP, PC, WB)	NA	NA
Hemostatic agents		
TXA	2 (2.7)	1 (6.3)
Outcomes		
Death (overall), n (%)	7 (9.7)	3 (18.8)
GOS-E (6 months), median (IQR)	7 (6 to 8)	5 (2 to 7.5)

Neuroworsening was defined as follows: (1) a decrease in the GCS motor score of 2 or more points, (2) a new loss of pupillary reactivity or development of pupillary asymmetry ≥2 mm, or (3) deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention. Shock index was calculated as follows: heart rate (bpm) divided by SBP (mm Hg). Patients with iTBI with AIS_{Brain} 6 were not included.

AIS Abbreviated Injury Scale, *aPTT* activated partial thromboplastin time, *CT* computed tomography, *ED* emergency department, *FFP* fresh frozen plasma, *GCS* Glasgow Coma Scale, *GOS-E* Glasgow Outcome Score Extended, *INR* international normalized ratio, *iTBI* isolated traumatic brain injury, *NA* not available, *PC* platelet concentrate, *PCC* prothrombin complex concentrate, *RBC* red blood cells, *SBP* systolic blood pressure, *TXA* tranexamic acid, *WB* whole blood

*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$: statistically significant differences between patients with iTBI with INR <1.2 and patients with iTBI with INR ≥1.2.

The results from the blood sample analyses were matched with the clinical and routine laboratory data of corresponding patients with iTBI for a study cohort of 88 patients who were then stratified according to admission INR (Fig. 1). The basic demographics and injury characteristics of the patients included in the analysis are shown in Table 1. Almost all patients had sustained a blunt trauma mechanism, with high velocity trauma as the most common cause of injury (44%) in patients with INR ≥ 1.2, followed by ground-level falls (34%) in patients with INR < 1.2 (Table 2). In more than 90% of cases, the iTBI was moderate to severe ($AIS_{Brain} \geq 3$) and closed (Table 1). Patients with INR ≥ 1.2, in general, were younger, were more shocked, and had presented with a lower Glasgow Coma Scale score. PIH as detected by CT was observed more frequent with abnormal INR. Midline shifts on CT were seen twice as frequently in patients with INR ≥ 1.2 (Table 1). Overall death increased with increasing INR as the median GOS-E at 6 months decreased (Table 1). In addition, 3.4% of the entire cohort of patients with iTBI had received hemostatic agents in the form of tranexamic acid (TXA), whereas just one patient with an INR ≥ 1.2 had been treated with TXA upon emergency department admission (Table 1).

Hemostatic Changes with Increasing INR

The majority of the results from CCAs and coagulation factor concentrations, except for aPTT, thrombin time, and fibrinogen, decreased with increasing INR (Table 3). Whereas thrombin time and fibrinogen levels did not change with increasing INR, the aPTT was significantly prolonged in those patients (Table 3). The activity of coagulation factors V, VIII, IX, and XIII dropped between 10 and 25% with INR ≥ 1.2, whereas protein C and S levels fell by approximately 20%. Coagulation factor V displayed the greatest decline with 25% with INR ≥ 1.2. Also with increasing INR, thrombin generation potential became impaired, as reflected by lower peak height as well as significantly lower ETP (Fig. 2A, B). Conversely, the amount of fibrin monomers increased with increasing INR, whereas D-dimer levels rose significantly from a mean of 943 µg/L in patients with INR < 1.2 to 1,301 µg/L in patients with INR ≥ 1.2 (Fig. 2C, Table 3).

Fibrinolytic Markers with Increasing INR

Fibrinolysis inhibitor PAI-1 remained largely unaltered across the two groups (Fig. 3C), whereas TAFI tended to be lower with INR ≥ 1.2 (Fig. 3A). Similarly, plasmin inhibitor antiplasmin decreased with increasing INR (Fig. 3B). In correspondence, plasminogen activity significantly decreased by 15% in patients with INR ≥ 1.2 (Table 3).

Discussion

The results from the present study provide more detailed insights into the complex mechanisms behind the various hemostatic abnormalities occurring with and after TBI. Blood samples collected from patients with iTBI after admission to 9 of 60 recruiting CENTER-TBI study sites across Europe were submitted and used for more in-depth analyses of the coagulation system beyond those routinely used to characterize hemostatic abnormalities. The INR was used as a crude a priori way to stratify for the presence or absence of a coagulation deficit on emergency department admission [8].

Increasing INR was associated with a 1.2-fold decrease in thrombin formation peak height and ETP. This is most likely explained by the reduction of coagulation factors V and VIII in these patients because ETP is strongly dependent on these factors. The activity of coagulation factors V, VIII, and IX dropped by 10–25% of their activity with increasing INR. Coagulation factor V, in its active form, is part of the prothrombinase complex, which catalyzes the conversion of prothrombin (factor II) into thrombin (factor IIa), whereas coagulation factor IX is part of the intrinsic tenase complex, which activates prothrombinase. Also observed in the present study was a decrease in activity of coagulation factor XIII by 15% with increasing INR, which can most likely be linked to an increased activation and consumption of coagulation

Table 2 Mechanism of injury in patients with iTBI stratified by INR ($n = 44$)

Injury Mechanisms	INR <1.2 ($n = 35$)	INR ≥1.2 ($n = 9$)
High-velocity trauma, n (%)	6 (17)	4 (44)
Blow to head (direct impact), n (%)	5 (14)	NA
Head against object (direct impact), n (%)	2 (5.7)	1 (11)
Ground-level fall, n (%)	12 (34)	2 (22)
Fall from height (>1 m), n (%)	8 (23)	1 (11)
Other closed head injury, n (%)	2 (5.7)	1 (11)

Data on mechanism of injury were missing for $n = 44$ patients with iTBI.

INR international normalized ratio, *iTBI* isolated traumatic brain injury, *NA* not available.

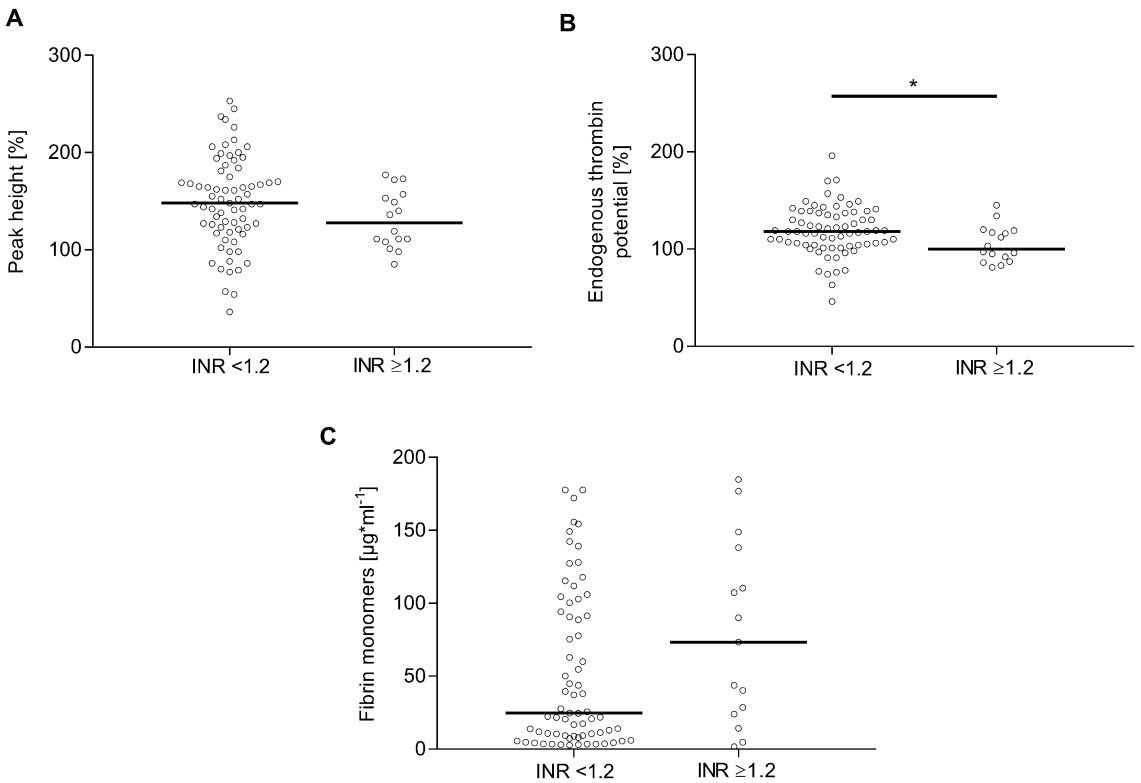

Fig. 2 Analysis of thrombin activity and generation in plasma of patients with iTBI stratified by INR. Peak height (**A**), endogenous thrombin potential (**B**), and fibrin monomers (**C**) were measured after iTBI by using calibrated automated thrombography. Statistically significant differences between patients with iTBI with INR < 1.2 and patients with iTBI with INR ≥ 1.2 are marked with asterisks (*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$). INR international normalized ratio, iTBI isolated traumatic brain injury

Table 3 Conventional coagulation parameters, coagulation factor activity and anticoagulant proteins of patients with iTBI stratified by INR ($n = 88$)

	INR <1.2 ($n = 72$)	INR ≥1.2 ($n = 16$)
Conventional coagulation parameters, median (IQR)		
Quick (%) (reference range 70–130)	101.0 (90.0–109.0)	74.0 (69.3–77.8)***
aPTT (seconds) (reference range 23–36)	28.1 (25.1–30.5)	32.0 (30.0–35.2)***
Thrombin time (seconds) (reference range 10–17)	14.0 (13.0–15.0)	14.0 (13.3–15.0)
Fibrinogen (mg/dL) (reference range 276–471)	371.0 (315.0–462.0)	389.0 (299.3–504.5)
Antithrombin (%) (reference range 83–128)	99.5 (89.3–113.0)	94.0 (84.8–103.3)*
Coagulation factors and anticoagulant proteins, median (IQR)		
Factor V (%) (reference range 62–139)	94.5 (79.3–110.8)	70.5 (51.3–78.8)***
Factor VIII (%) (reference range 50–150)	136.5 (111.8–175.5)	119.0 (100.3–169.8)
Factor IX (%) (reference range 65–150)	113.0 (99.5–128.8)	100.5 (85.3–122.3)
Factor XIII antigen (%) (reference range 75.2–154.8)	88.0 (75.0–104.0)	68.0 (61.5–83.0)**
Protein C (%) (reference range 70.0–140.0)	98.0 (86.0–112.0)	82.5 (69.3–92.0)**
Protein S (%) (reference range 63.5–149)	98.5 (81.8–118.3)	77.5 (67.2–96.3)**
D–dimer (µg/L) (reference range 0–232)	943.0 (418.0–1,300.5)	1,301.5 (966.0–6,260.5)*
Plasminogen (%) (reference range 80–133)	89.0 (79.0–97.3)	76.5 (60.0–83.8)**

Conventional coagulation parameters, coagulation factors, and anticoagulant proteins of patients with iTBI are represented as median and IQR

aPTT activated partial thromboplastin time, *INR* international normalized ratio, *IQR* interquartile range, i*TBI* isolated traumatic brain injury

*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$: statistically significant differences between patients with iTBI with INR <1.2 and those with INR ≥1.2

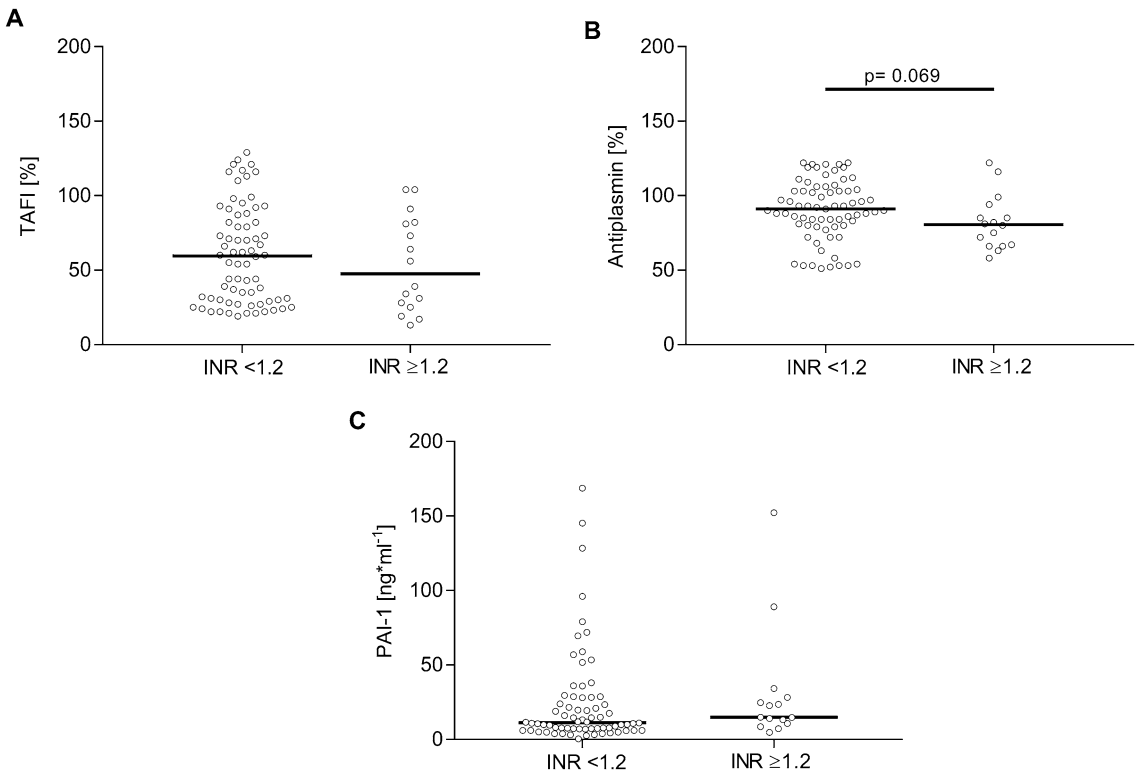

Fig. 3 Analysis of fibrinolytic regulators in plasma of patients with iTBI stratified by INR. TAFI (**A**), antiplasmin (**B**), and PAI-1 (**C**) were measured following iTBI. Statistically significant differences between patients with iTBI with INR < 1.2 and patients with iTBI with INR ≥ 1.2 are marked with asterisks (*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$). INR international normalized ratio, iTBI isolated traumatic brain injury, PAI-1 plasminogen activator inhibitor 1, TAFI thrombin-activated fibrinolysis inhibitor

factors, thus coagulation factor XIII was depleted. Coagulation factor XIII is activated by thrombin to cross-link fibrin. A deficiency of coagulation factor XIII is known to worsen clot stability and increase bleeding tendency [9].

The reduced activity of thrombin-dependent factors, such as V, VIII, and XIII, may suggest impaired clot formation in iTBI with a bleeding phenotype. The authors of several studies have reported elevated thrombin generation and thrombin-generation-associated markers within 6 and 12 h following iTBI [10–12]. However, Massaro and co-workers [13] have shown a progressive and delayed procoagulant state after 48 h of injury in iTBI using thromboelastography. Thus, the decrease in thrombin activity observed in the present study indicates a consumption of thrombin, which may be caused by severe consumption of coagulation factors. Accordingly, the concentration of fibrin monomers increased with INR up to 3.0-fold with INR ≥ 1.2, whereas the activity of antithrombin decreased. A recent prospective study demonstrated that high fibrin monomer levels on admission in severe iTBI was associated with progression of hemorrhage [14]. High concentrations of fibrin monomers were observed in patients with hemostatic abnormalities (e.g., disseminated intravascular coagulation and deep vein thrombosis), and it seems promising to further evaluate the procoagulant status in these patients [15].

In a prospective study in severely injured patients with iTBI, the authors reported a reduction of antithrombin levels, which was associated with increased clot strength due to high fibrinogen concentration in the subacute phase (between days 5 and 7) after iTBI [16]. In the present study, fibrinogen levels were not depleted with increasing INR. It was concluded that a procoagulant status may occur during different phases after severe TBI [16]. Moreover, clinical data indicated the presence of severe brain injuries ($AIS_{Brain} \geq 4$) in about 80% with PIH. An earlier study in critically injured trauma patients demonstrated a higher risk of thromboembolic complications with decreased antithrombin activity in those patients [17].

The balance between coagulation and fibrinolysis determines the stability of the fibrin clot. Apart from the aforementioned properties, thrombin is also involved in stabilizing the clot by activating TAFI. Alterations in thrombin generation and activation of TAFI will therefore directly affect the stabilization of clots against lysis

[18, 19]. In the present study, reduced thrombin generation was associated with decreased activation of TAFI in patients with INR ≥ 1.2, which might have had a direct impact on clot protection against lysis.

In the present study, PAI-1 levels in plasma remained largely unaltered. PAI-1 is mainly produced by the endothelium and acts as a principal inhibitor of tissue plasminogen activator (tPA). According to the clinical data, patients suffered neither from hypoperfusion nor from shock, both of which are known triggers of the protein C pathway. This pathway inhibits PAI-1, leading to less inhibition of tPA, with the overall effect to promote lysis. In the experimental setting, TBI has been shown to initiate fibrinolysis, independent of shock and hypoperfusion, by releasing tPA and urokinase plasminogen activator from contused brain tissue [20]. It has also been shown that tPA activity is increased by approximately 30% within 1–3 h post TBI and returns to baseline levels by 24 h post TBI [21]. In the present study, plasminogen, which is cleaved by tPA to generate plasmin, decreased to 76% activity with increasing INR, potentially indicating enhanced conversion into plasmin. At the same time, antiplasmin activity also declined with increasing INR. These observations, together with the decreased activation of TAFI in INR ≥ 1.2, are suggestive of increased fibrinolysis, as evidenced by increasing D-dimer levels with increasing INR. It may be precluded that TXA had an influence on fibrinolysis in patients with iTBI with increasing INR because of the restricted number of patients who actually had received the agent. Endogenous release of tPA from contused brain tissue may be a distinct trigger to promote coagulopathy in iTBI apart from hemostatic abnormalities seen in the general trauma population.

The present study also suggests an activation of the protein C pathway, independent of shock and hypoperfusion, to further promote lysis, as evidenced by reductions in pathway-associated proteins (e.g., protein S, coagulation factors V and X [indirect measurement of factor X], and protein C) itself with increasing INR. Low protein C levels have previously been reported in patients with iTBI and trauma patients with hypoperfusion and were associated with poor outcome [22, 23].

There is also retrospective evidence for patients with iTBI with high D-dimer levels in plasma being at higher risk for progressive hemorrhagic injury (PHI) and worse outcomes [24, 25]. In the present study, PHI, which included the enlargement of both extradural and subdural hematoma (25% and 43.7% in patients with INR ≥ 1.2 vs. 20.8% and 38.8% in patients with INR < 1.2, respectively) and subarachnoid hemorrhage (50% in patients with INR ≥ 1.2 vs. 47.2% in patients with INR < 1.2), could be observed in patients with iTBI with elevated INR. In addition, mortality and unfavorable 6-month outcomes (GOS-E) increased with increasing INR. Several studies have previously confirmed D-dimer to predict PHI as well as correlations between elevated D-dimer levels and unfavorable outcomes, longer in-hospital stay, and higher mortality in patients with iTBI [25–28].

Although all efforts were undertaken to mirror early changes within the coagulation system in patients with iTBI, the major limitation of the present study remains the fairly large time window of patient inclusion into the CENTER-TBI core study. This precluded a stricter timeline for blood sampling after admission. In addition, blood sampling did not follow a timeline-guided protocol specifying exact time points, thereby causing variation between study centers that contributed to this study. The median time interval between injury and first blood sampling in the present study was 13.1 h (interquartile range 6.2–20.8 h). It is well accepted that hemostatic abnormalities after TBI occur quickly after the initial impact and follow dynamic patterns involving both hypercoagulative and hypocoagulative states with potential overlap [10]. Whether these findings may be interpreted as maladaptive/pathologic or represent a physiologic response to the impact remains unknown. The observation that thrombin generation and TAFI were both reduced in patients with INR ≥ 1.2 could be interpreted as a protection against lysis. Hemostatic and/or resuscitation therapies in addition to emergency procedures during acute care might have had a theoretical impact on the present results, although the focus of the analysis was given to early acute and thus mostly undiluted blood samples. In addition, prehospital care was not documented in detail in the CENTER-TBI central database. Although the present work initially aimed to present a more detailed picture of the possible underlying mechanistic changes/exchanges in hemostasis after iTBI, including outcomes, the study remains rather descriptive. Nevertheless, we observed in the present study distinct patterns involving key pathways of the highly complex and dynamic coagulation system in patients with iTBI that offer windows of opportunity for further research.

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Author contributions
Data were acquired, analyzed, and interpreted by JKB, VS, ST, HG, NS, and MM. Statistical expertise was provided by RL. HS, JZ, OG, RR, SS, and NC contributed to the conception of the study, provided scientific support, and critically revised the data. The manuscript was written by JKB and was critically reviewed by all authors. Supervision was provided by MM. All authors read and approved the final manuscript.

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Conflict of interest
The authors declare that they have no conflict of interest regarding this article.

Ethics approval/informed consent
As part of the CENTER-TBI core study, the present analysis was performed in accordance with relevant local ethics and European law.

Appendix

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