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CRITICAL CARE

Prevalence and impact of abnormal ROTEM® assays in severe blunt trauma: results of the 'Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study'

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Editor's key points

- In a cohort study of blunt trauma, impact of abnormal ROTEM® assays was evaluated.
- At defined thresholds for ROTEM®, significant differences in mortality were seen.
- Maintaining fibrin polymerization and treating hyperfibrinolysis may improve outcome in trauma patients.
- This study adds to the evidence that ROTEM® assays are useful in managing trauma patients.

Background. ROTEM®/TEG® (rotational thromboelastometry) assays appear to be useful for the treatment of bleeding trauma patients. However, data on the prevalence and impact of abnormal ROTEM® assays are scarce.

Methods. This is a prospective cohort study of blunt trauma patients (Injury Severity Score ≥15 or Glasgow Coma Score ≤14) admitted to Innsbruck Medical University Hospital between July 2005 and July 2008. Standard coagulation tests, antithrombin (AT), prothrombin fragments (F1+2), thrombin–antithrombin complex (TAT), and ROTEM® assays were measured after admission. Data on 334 patients remained for final analysis.

Results. ROTEM® parameters correlated with standard coagulation tests (all Spearman $r>0.5$), and significant differences in mortality were detected for defined ROTEM® thresholds [FIBTEM 7 mm (21% *vs* 9%, $P=0.006$), EXTEM MCF (maximum clot firmness) 45 mm (25.4% *vs* 9.4%, $P=0.001$)]. EXTEM MCF was independently associated with early mortality [odds ratio (OR) 0.94, 95% confidence interval (CI) 0.9–0.99] and MCF FIBTEM with need for red blood cell transfusion (OR 0.92, 95% CI 0.87–0.98). In polytrauma patients with or without head injury ($n=274$), the prevalence of low fibrinogen concentrations, impaired fibrin polymerization, and reduced clot firmness was 26%, 30%, and 22%, respectively, and thus higher than the prolonged international normalized ratio (14%). Hyperfibrinolysis increased fatality rates and occurred as frequently in isolated brain injury ($n=60$) as in polytrauma ($n=274$) (5%, 95% CI 1.04–13.92 *vs* 7.3%, 95% CI 4.52–11.05). All patients showed elevated F1+2 and TAT and low AT levels, indicating increased thrombin formation.

Conclusions. Our data enlarge the body of evidence showing that ROTEM® assays are useful in trauma patients. Treatment concepts should focus on maintaining fibrin polymerization and treating hyperfibrinolysis.

Keywords: blood, coagulation; measurement technique, thrombelastograph, thrombelastometry, trauma

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Guidelines for managing trauma-induced coagulopathy (TIC) recommend administration of fresh-frozen plasma (FFP) according to measurements of prothrombin time (PT) and activated partial thrombin time, although these tests have never been validated for estimating bleeding tendency or treatment of haemorrhage-induced coagulopathy and cannot reflect quality of clot formation.[1–3] Because strategies for treating the main underlying pathologies of acquired coagulopathy, namely thrombin deficiency, poor clot firmness, and hyperfibrinolysis, are different, knowledge of primary deficiencies is of clinical importance. While thrombin formation has been shown to be sustained in the early phase of severe trauma,[4 5] fibrinogen and platelets are consumed by the clot formation process itself. Furthermore, blood loss, dilution, acidosis, and hypothermia, commonly present in injured patients, additionally decrease concentrations of fibrinogen and numbers of platelets.[6] Therefore, we hypothesize that on admission, severely injured patients more frequently exhibit low clot firmness and poor fibrin polymerization than impaired thrombin formation.

In contrast to plasmatic coagulation tests, viscoelastic assays like ROTEM®/TEG® can estimate speed and quality of clot formation, including detection of hyperfibrinolysis, and are performed in whole blood, thus closely reflecting the *in vivo* situation.[7] However, so far, only few studies including small patient populations have reported on viscoelastic measurements in trauma patients,[8–11] and studies focusing on patients with isolated head trauma, who might show specific pathology, are lacking.

Using rotational thromboelastometry (ROTEM®) assays, we tested the hypothesis that on Emergency Department admission, severely injured patients more frequently exhibit low clot firmness and poor fibrin polymerization than impaired thrombin formation. Aside from ROTEM® assays, standard coagulation tests, antithrombin (AT) concentrations, and molecular markers of thrombin formation were measured simultaneously in this prospective cohort study enrolling 334 patients with either polytrauma (n=274) or isolated head injury (n=60). As secondary endpoints, plasmatic test results were compared with viscoelastic parameters; prevalence and outcome of hyperfibrinolysis were determined; and the association between viscoelastic parameters and early mortality and need for red blood cell (RBC) transfusion was analysed.

Methods

The Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study was conducted as a single-centre, prospective, cohort study including adult polytrauma patients, who were admitted to the Level I Trauma Center at Innsbruck Medical University Hospital between July 2005 and July 2008. Starting in January 2006, patients with isolated traumatic brain injury were enrolled as well.

Severe polytrauma was defined as an Injury Severity Score (ISS) of $\geq$15 resulting from injury of at least two body regions. Isolated head injury was defined as a Glasgow Coma Score of $\leq$14 after blunt head trauma in patients with an Abbreviated Injury Score (AIS) of $<$3 in any other body region.

Patients $<$18 yr, with penetrating injuries, who were admitted to the study hospital later than 12 h after trauma, who had pre-existing coagulopathy, burn injury, malignant disease, were avalanche victims, or exhibited non-head single trauma were excluded.

The study protocol was approved by the Ethics Committee of Innsbruck Medical University. The need for written informed consent was waived because study-related blood sampling was judged a minimal-risk intervention and all patients were treated according to routine institutional treatment guidelines.

Blood sampling and analysis

After ISS/Glasgow Coma Scale (GCS) calculation immediately after Emergency Department admission, blood was drawn from all patients into citrated tubes and sent to the central laboratory for immediate workup or centrifugation and storage at -80°C. Samples were analysed and ROTEM® assays performed by specialized laboratory personnel unaware of patient details. All test kits were from Siemens Healthcare AG, Erlangen, Germany, and were used for the following assays: PT (Thromborel S®, reference range 70–130%), activated partial thromboplastin time (aPTT, Pathromtin SL®, reference range 26–37 s), antithrombin III (AT, Berichrom ATIII®, reference range 75–125%), fibrinogen concentration (Multifibren®, reference range 180–350 mg dl^{-1}), prothrombin fragment (F1+2, Enzygnost® F1+2, reference range 70–230 pmol litre^{-1}), thrombin–antithrombin complex (TAT, Enzygnost® TAT micro, reference range 1–4.1 μg litre^{-1}), D-Dimer (DD, chromogenic latex immunoassay DD, STA Roche Diagnostics, Mannheim, Germany, reference range 0–190 μg litre^{-1}; Innovance D-Dimer® Siemens Healthcare AG, reference range 0–500 μg litre^{-1}). DD ratio was calculated by dividing the measured value by the upper normal value of the used assay.

Viscoelastic measurements were performed using rotational thrombelastometry [ROTEM®, Tem Innovations GmbH (formerly Pentapharm), Munich, Germany] and the extrinsically activated assays (EXTEM®, FIBTEM®).

EXTEM® coagulation time (CT, reference range $<$80 s) reflects initiation of coagulation after mild activation with tissue factor depending on concentrations of coagulation factors and fibrinogen. Clot formation time (CFT, reference range $<$150 s) describes the time needed to reach a clot strength of 20 mm, depending on thrombin formation, fibrin formation, and platelets. Maximum clot firmness (EXTEM MCF, reference range 50–72 mm) describes the maximal recorded clot strength during 60 min, which mainly depends on numbers and function of platelets and fibrin formation. By adding the platelet-blocking substance cytochalasin D (FIBTEM® assay), fibrinogen's contribution to clot strength can be measured separately (FIBTEM MCF; reference range 9–25 mm). The lysis index 30 min (LI30, %) and lysis index 60 min (LI60, reference range $\geq$85%) describe the percentage of maximum clot strength present at 30 and 60 min.

Critical values for ROTEM® parameters were defined according to 15 yr of clinical experience with ROTEM® assays showing occurrence of diffuse microvascular bleeding at thresholds of EXTEM CT$>$100 s, CFT$>$200 s, MCF$<$45 mm, and FIBTEM MCF$<$7 mm.

Transfusion of blood components and administration of coagulation factor concentrates

As in clinical routine, bleeding patients were managed according to plasmatic tests, ROTEM® measurements, or both and by clinical decision in urgent cases. Coagulation factor concentrates were used first in most cases until FFP was available.

Usual thresholds for treating coagulopathy with coagulation factor concentrates, FFP, and platelets were PT $<$50% (international normalized ratio, INR$>$1.5), aPTT $>$50 s, fibrinogen concentration $<$150 mg dl^{-1}, platelet count $<$100 G litre^{-1}, EXTEM CT$>$100 s, EXTEM MCF$<$45 mm, and FIBTEM MCF$<$7 mm. A haemoglobin below 8–9 mg dl^{-1} was the

usual threshold for administering RBCs. No patient received antifibrinolytics prophylactically.

Data collection

Patient characteristics, type of injury, ISS, GCS, amount and type of fluids administered before Emergency Department admission, and time elapsed between trauma and study hospital admission were documented at Emergency Department admission, as were arterial pressure, heart rate, blood cell count, pH, lactate, and base excess (BE). Furthermore, type and numbers of transfused blood components and dosage of coagulation factors administered were registered 4, 6, and 24 h thereafter. Early mortality was defined as death occurring within the first 24 h after Emergency Department admission. All study patients were followed until hospital discharge, and 30 day mortality was recorded.

Statistical analysis

The SPSS software package (Version 17.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was applied to test for normal distribution of study variables. Because several variables departed significantly from normal at an α-level of 0.05, non-parametric tests and Spearman's rank correlation were used throughout the analyses. The Kruskal–Wallis test and the Mann–Whitney *U*-test were used to analyse metric data; for categorical data, the χ^2 test and Fisher's exact test were used, as applicable.

Logistic regression models were used to identify coagulation tests independently associated with early death and need for RBC transfusion. Regression models were adjusted for severity of tissue hypoperfusion (assessed by base deficit and haemoglobin levels; early death) or injury severity (assessed by ISS; RBC transfusion 6 h). Unadjusted logistic regression models were used to identify the contribution of blood component transfusion to early mortality. Receiver operating characteristic (ROC) analysis was performed to estimate the area under the curve (AUC) for fibrinogen platelets and PT to predict poor clot firmness (EXTEM MCF $<$45 mm) and determine thresholds (maximum sum of sensitivity and specificity) for ROTEM® parameters, which in logistic regression models proved to be associated with early mortality and need for RBC transfusion.

P-values of $<$0.05 were deemed to indicate statistical significance. Data are presented as median values with interquartile ranges (IQR), if not otherwise indicated.

Results

During the 36 month study period, 403 patients were enrolled; 69 had to be excluded secondarily because of *post hoc* verified exclusion criteria [ISS $<$15 (n=36), age $<$18 yr (n=16), isolated non-head injury (n=6), intake of warfarin/platelet aggregation inhibitors (n=3), avalanche victim (n=3), isolated burn injury (n=1), pre-existing haematological or malignant disease (n=2), presence of basilar vein thrombosis (n=1), or delayed admission to study hospital (n=1)].

Clinical characteristics of the 334 trauma patients included in the final analysis are shown in Table 1. Because comparison of the patients in the polytrauma group who either showed concomitant head injury or not revealed no clinically relevant differences regarding clinical characteristics or laboratory data at admission (data not shown), data were pooled and analysed as the group of polytrauma patients and compared with those of patients exhibiting isolated brain injury (GCS$\leq$14, AIS other body regions $<$3).

Polytrauma patients more frequently presented with systolic arterial pressure below 95 mm Hg, had received more i.v. fluids prehospital and also received more blood transfusions and coagulation factor concentrates during the first 6 h than did those with isolated brain injury. However, the incidence of acidosis and low BE was similar in all trauma patients. Twenty-six patients died within the first 24 h after arrival at the study centre. The two causes of early death were haemorrhagic shock (n=13) and severe head injury (n=13). Causes of 30 day mortality were brain death (n=16), multi-organ dysfunction syndrome (n=4), and secondary haemorrhage (n=1).

Prevalence of clinically relevant abnormal plasmatic and viscoelastic coagulation

Patients with isolated brain injury less frequently showed impaired test results without a predominant pattern of deficiencies (Fig. 1, black lines). However, when compared with polytrauma patients (Fig. 1, red lines), they showed similar measurements of prothrombin fragments and platelet counts; hyperfibrinolysis was diagnosed in 5% [95% confidence interval (CI) 1.04–13.92], thus as frequently as in patients with multiple injuries (Table 2).

In polytrauma patients, fibrinogen deficiency (26%) was more frequently observed than abnormal plasmatic (INR 14%, aPTT 11%), viscoelastic clotting times (EXTEM CT 12%) or low platelet count (4%). Slowed clot formation speed, reduced clot firmness, and impaired fibrin polymerization occurred frequently with a prevalence of 23%, 22%, and 30%, respectively (Fig. 1). ROTEM® results changed with injury severity [ISS 15–29 (n=104), 30–50 (n=116) or 50–75 (n=54)], as did measurements of standard coagulation tests and BE (Fig. 2).

Correlations between ROTEM® and plasmatic coagulation tests

In all patients, ROTEM® parameters correlated significantly with standard coagulation tests (Table 3). TAT and F1+2 correlated significantly only with each other and with DD ratio (r=0.611, 0.587, respectively, $P$$<$0.001).

PT [AUC ROC (95% CI), 0.83 (0.78–0.89)], fibrinogen concentrations [0.89 (0.84–0.93)], and platelet count [0.84 (0.79–0.9)] predicted MCF in EXTEM to be $<$45 mm. Corresponding cut-off values (maximum sum of sensitivity and

Table 1 Clinical characteristics at admission, percentage of trauma patients receiving blood components and coagulation factor concentrates within 6 h and outcome of study patients. ED, emergency department; ISS, Injury Severity Score; GCS, Glasgow Coma Scale; SAP, systolic arterial pressure; BE, base deficiency; RBC, red blood cell concentrate; FFP, fresh-frozen plasma; PC, apheresis platelet concentrate; FI concentrate, fibrinogen concentrate; PCC, prothrombin complex concentrate (FII, FVII, FIX, FX). Data are shown as median (IQR) or *n* (percentage)

	All	Isolated brain injury	Polytrauma	*P*-value
Clinical characteristics				
n	334	60	274	
Age (yr)	43 (27, 56)	48 (32, 67)	42 (27, 54)	0.022
Male patients (*n*)	260 (77.8)	42 (70.0)	218 (79.6)	0.106
Time to ED (min)	75 (55, 120)	60 (45, 106)	75 (60, 120)	0.106
ISS (points)	34 (24, 45)	25 (16, 29)	35 (25, 50)	<0.001
GCS (points)	11 (6,15)	7 (3, 9)	13 (6, 15)	<0.001
SAP<95 mm Hg (*n*)	53 (15.9)	3 (5.0)	50 (18.2)	0.013
BE< −6 mmol litre^{-1} (*n*)	72 (21.6)	14 (23.3)	58 (21.2)	0.702
pH≤7.3 (*n*)	95 (28.4)	12 (20.0)	83 (30.3)	0.350
Crystalloids (ml)	1000 (500, 1500)	500 (500, 1000)	1000 (500, 1500)	<0.001
Colloids (ml)	500 (0, 500)	0 (0, 0)	500 (0, 1000)	<0.001
Surgery within 4 h (*n*)	170 (50.9)	25 (41.7)	145 (52.9)	0.021
Percentage of trauma patients and outcome				
RBC 6 h	125 (37.4)	9 (15)	116 (42.3)	<0.001
FFP 6 h	77 (23.1)	2 (3.3)	75 (27.4)	<0.001
PC 6 h	41 (12.3)	2 (3.3)	39 (14.2)	0.020
FI concentrate 6 h	157 (47)	9 (15)	148 (54)	<0.001
PCC 6 h	74 (22.2)	4 (6.7)	70 (25.5)	0.002
Early death (24 h, *n*)	26 (7.8)	5 (8.3)	21 (7.7%)	0.861
Total mortality (*n*)	47 (14.1)	12 (20.0)	35 (12.8)	0.055

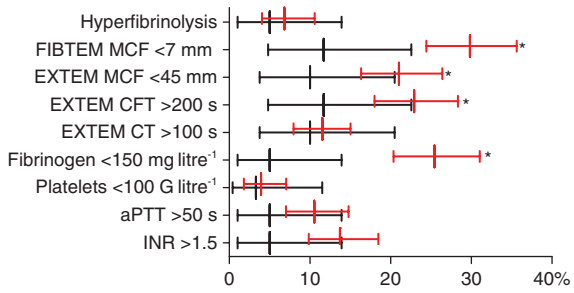

Fig 1 Prevalence (95% CI) of clinically relevant abnormal coagulation tests in patients with isolated brain injury (black lines, *n*=60) and those with polytrauma (red lines, *n*=274). Extrinsically activated ROTEM® parameters are FIBTEM MCF, EXTEM MCF, EXTEM CFT, and EXTEM CT. Standard laboratory parameters are fibrinogen concentration (fibrinogen), platelet count (platelets), aPTT, and INR. *P<0.05 polytrauma *vs* isolated brain injury (Fisher's exact test)

specificity) were 68% (sensitivity 72%, specificity 76%), 151 mg dl^{-1} (sensitivity 86%, specificity 71%), and 147 G litre^{-1} (sensitivity 79%, specificity 78%) for PT, fibrinogen concentrations, and platelet count, respectively.

Incidence of hyperfibrinolysis

According to ROTEM® tracings, 23 of the 334 study patients (6.9%, 95% CI 4.42–10.15) showed hyperfibrinolysis at admission. Fourteen cases were classified as fulminant hyperfibrinolysis showing complete dissolution of the clot within 60 min, while nine patients showed reduction of clot firmness of 16–35%. Two of these patients received tranexamic acid. Overall mortality of patients exhibiting hyperfibrinolysis was 56.5% (13/23); for moderate and fulminant hyperfibrinolysis, it was 11.1% (1/9) and 85.7% (12/14), respectively.

Patients with hyperfibrinolysis had higher ISS [median (IQR) 75 (34, 75) *vs* 33 (24, 43), P<0.001] and lower GCS scores [6 (3, 13) *vs* 11 (6, 15), P=0.015], showed lower systolic arterial pressure [100 (65, 120) *vs* 120 (109, 140) mm Hg, P=0.001], pH [7.28 (7.11, 7.34) *vs* 7.34 (7.29, 7.39), P=0.001], BE [−7.9 (−13.9, −4.3) *vs* −3.2 (−5.9, −1.3) mmol litre^{-1}, P>0.001] and higher lactate levels [4.22 (2.3, 7.4) *vs* 2.2 (1.6, 3.2) mmol litre^{-1}, P=0.002] than did patients without hyperfibrinolysis. The incidence of hyperfibrinolysis was greater in trauma patients with concomitant abdominal trauma (16/153, 10.5%) than in those without (7/179, 3.9%) (P=0.019), while no differences were observed for the presence or absence of concomitant brain, chest, or limb injury.

Table 2 Standard laboratory parameters, molecular markers of thrombin formation and viscoelastic parameters of 334 patients with blunt trauma at admission. Data are shown as median (IQR). BE, base excess; PT, prothrombin time; aPTT, activated partial prothrombin time; DD ratio, D-Dimer ratio, haemoglobin; TAT, thrombin–antithrombin complex; F1+2, prothrombin fragments F1+2. EXTEM, extrinsically activated ROTEM® assay; CT, coagulation time; CFT, clot formation time; MCF, maximum clot firmness; FIBTEM MCF, fibrin polymerization

	Isolated head injury ($n=60$)	Polytrauma ($n=274$)	P-value
Laboratory parameters			
pH	7.37 (7.31, 7.41)	7.33 (7.28, 7.38)	0.004
BE (−2.0 to 2.0 mmol litre^{-1})	−2.8 (−6.1, −0.5)	−3.5 (−6.07, −1.6)	0.206
Lactate (0.44–2 mmol litre^{-1})	2.22 (1.33, 3.66)	2.28 (1.65, 3.4)	0.681
Haemoglobin (13.0–17.7 g dl^{-1})	12.5 (11.3, 13.9)	11.3 (9.4, 12.8)	<0.001
Platelets (150–380 G litre^{-1})	174 (156, 207)	169 (137, 202)	0.157
PT (70–130%)	91 (82, 99)	75 (58, 89)	<0.001
aPTT (26–37 s)	31 (26, 34)	32 (29, 39)	0.001
Fibrinogen (200–350 mg dl^{-1})	248 (210, 299)	203 (148, 246)	<0.001
Antithrombin III (75–125%)	80 (68, 88)	66 (53, 79)	<0.001
DD ratio	6.1 (3.1, 11)	10.8 (5.4, 23.1)	<0.001
TAT (1–4.1 μg litre^{-1})	60 (39, 60)	60 (57, 60)	0.011
F1+2 (70–230 pmol litre^{-1})	1200 (1069, 1200)	1200 (1200, 1200)	0.159
Viscoelastic parameters			
CT EXTEM (42–78 s)	59 (53, 68)	64 (55, 75)	0.041
CFT EXTEM (53–144 s)	127 (101, 156)	147 (108, 199)	<0.001
MCF EXTEM (50–69 mm)	55 (50, 58)	51 (45, 56)	0.004
FIBTEM MCF (9–25 mm)	12 (9, 14)	9 (6, 13)	<0.001
Hyperfibrinolysis (n)	3 (5%)	20 (8.1%)	0.524

Association of coagulation tests with early (24 h) mortality and the need for RBC transfusion within 6 h

χ^2 statistics indicated significant differences in early mortality for values below or above defined ROTEM® thresholds: MCF of FIBTEM, 7 mm (21% *vs* 9%, $P=0.006$), clotting time of EXTEM, 100 s (45.5% *vs* 8.4%, $P<0.001$), CFT of EXTEM, 200 s (27% *vs* 8.7%, $P<0.001$), and MCF of EXTEM, 45 mm (25.4% *vs* 9.4%, $P=0.001$).

When adjusted for BE and haemoglobin levels, values of PT, EXTEM MCF, and LI60 were significantly associated with decreased risk for early death. In contrast, values of DD ratio, aPTT, EXTEM CT, and CFT significantly increased the risk for early death (Table 4). Transfusion of neither RBC (OR 0.967, 0.904–1.034), platelets (OR 0.836, 0.639–1.095), nor FFP (OR 0.069, 0.940–1.002) was significantly associated with early mortality. At thresholds close to those of predefined values, EXTEM CT, CFT, and MCF showed the maximum sum of sensitivity and specificity in predicting early mortality (all parameters AUC 0.8; EXTEM CT 91 s, CFT 218 s, MCF 46 mm).

Correlation analysis showed that numbers of all blood components correlated with each other, as did numbers of units transfused at 6 and 24 h (data not shown). Thus, we tested coagulation parameters for their prediction of RBC transfusion within 6 h and adjusted logistic regression analysis for ISS. PT, fibrinogen concentration, platelet numbers, and MCF FIBTEM were factors significantly associated with a reduced risk for RBC transfusion (Table 5). Cut-off values set at the maximum sum of sensitivity and specificity were 71% for PT, 182 mg dl^{-1} for fibrinogen concentration, and 7 mm for FIBTEM MCF.

Discussion

The results of this prospective cohort study show that when compared with standard coagulation tests, ROTEM® parameters accurately detect TIC and also proved to be independent factors associated with both mortality and RBC transfusion. Furthermore, critical thresholds defined from long-term clinical experience with ROTEM® assays in bleeding patients were confirmed as being associated with mortality and need for early RBC transfusion. Viscoelastic assays can be obtained within a few minutes, closely reflecting the *in vivo* situation and enabling differentiated diagnosis of primary underlying pathologies including hyperfibrinolysis. Plasmatic coagulation tests show a high sensitivity to detect even small changes in concentrations of activating coagulation factors, but results do not necessarily translate into bleeding cessation, because they only reflect initiation of coagulation. In fact, the predominantly observed pathologies in polytrauma patients were poor fibrinogen polymerization and EXTEM MCF, followed by hyperfibrinolysis and prolonged initiation of coagulation. Altogether, our data enlarge the body of evidence showing that viscoelastic assays are more appropriate than are standard coagulation assays for diagnosing and treating TIC in blunt trauma patients.[7–10 12]

In patients with isolated brain injury, the reported prevalence of coagulopathy, but also the definition of coagulopathy, varies widely, as summarized by Talving and

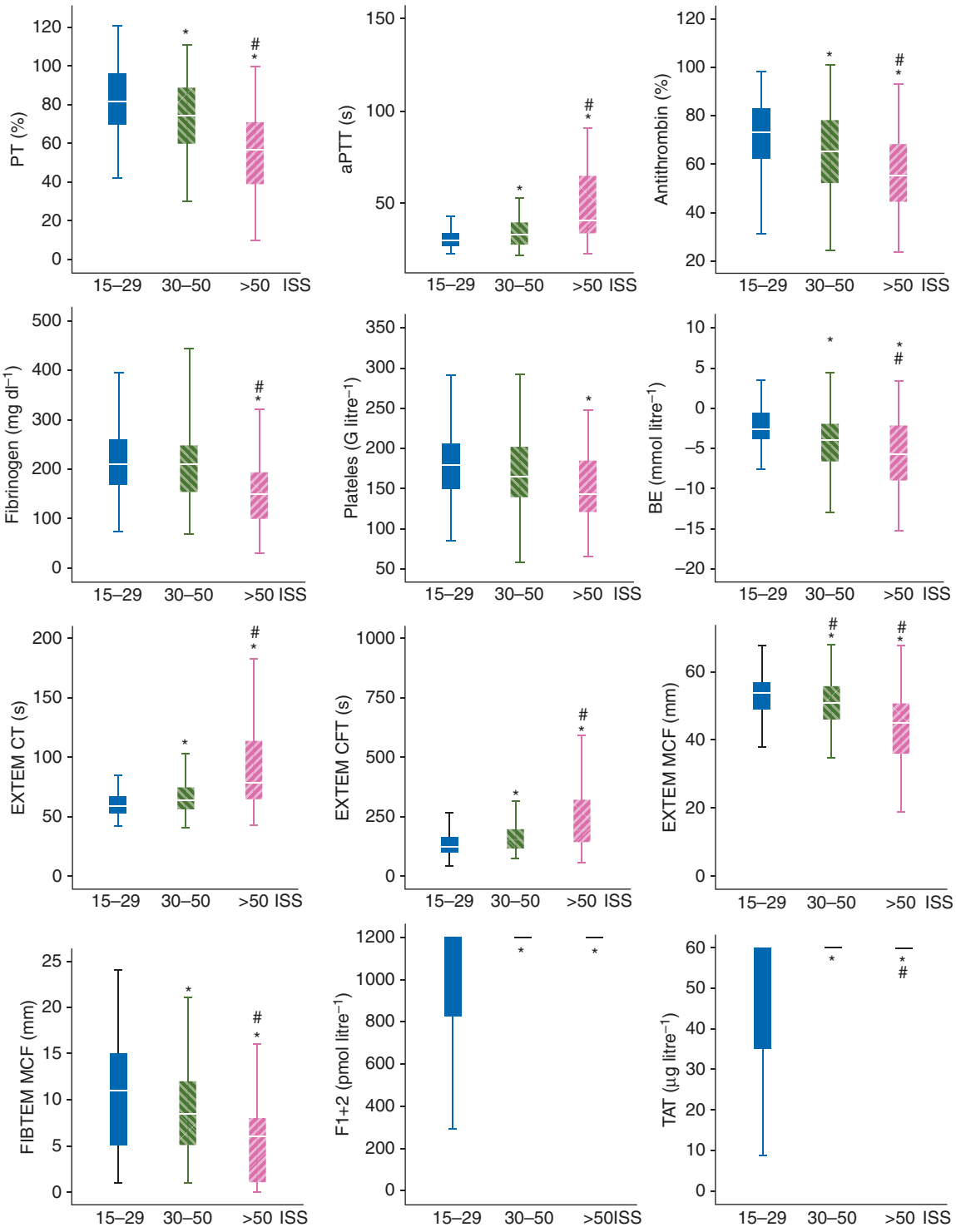

Fig 2 Relation of plasmatic test results [PT, aPTT, antithrombin activity (AT), fibrinogen concentration, platelet count], base excess (BE), extrinsically activated ROTEM® parameters (EXTEM CT, CFT, MCF, FIBTEM MCF), prothrombin fragments (F1+2) and TAT in polytrauma patients according to ISS grouped as ISS 15–29 (n=104), 30–50 (n=116), and 50–75 (n=54). The Kruskal–Wallis test and the Mann–Whitney U-tests were used for analysing differences between ISS groups. *$P<0.05$ when compared with the ISS group 15–29, #$P<0.05$ when compared with the ISS group 30–50.

Table 3 Correlations of ROTEM® parameters and plasmatic coagulation tests ($n=334$). PT, prothrombin time; aPTT, activated partial prothrombin time; EXTEM, extrinsically activated ROTEM® assay; CT, coagulation time; MCF, maximum clot firmness; FIBTEM MCF, fibrin polymerization

	Spearman rank correlation coefficient	*P*-value
EXTEM CT		
PT	−0.535	<0.001
EXTEM MCF		
PT	0.632	<0.001
fibrinogen	0.793	<0.001
platelet count	0.660	<0.001
FIBTEM MCF		
PT	0.694	<0.001
fibrinogen	0.811	<0.001
EXTEM MCF	0.841	<0.001
PT		
aPTT	−0.739	<0.001
fibrinogen	0.726	<0.001
AT	0.734	<0.001

Table 4 Summary of logistic regression models (adjusted for BE and haemoglobin) testing the independent influence of coagulation parameters on the probability of 24 h mortality in polytrauma patients. PT, prothrombin time; aPTT, activated partial prothrombin time; DD, D-Dimer; EXTEM, extrinsically activated ROTEM® assay; CT, coagulation time; CFT, clot formation time; MCF, maximum clot firmness; LI60, lysis index 60 min; FIBTEM MCF, fibrin polymerization

	Regression coefficient	*P*-value	Exp (*B*)	95% CI	
PT (%)	−0.50	0.005	0.951	0.919	0.985
aPTT (s)	0.27	0.002	1.027	1.010	1.045
DD ratio	0.51	0.001	1.053	1.021	1.086
Fibrinogen (mg dl^{-1})	−0.003	0.547	0.997	0.988	1.007
Platelets (G litre^{-1})	0.002	0.797	1.002	0.989	1.014
EXTEM CT (s)	0.010	0.036	1.010	1.001	1.019
EXTEM CFT (s)	0.001	0.017	1.001	1.000	1.002
EXTEM MCF (mm)	−0.61	0.022	0.940	0.892	0.991
EXTEM LI 60 (%)	−0.040	0.001	0.961	0.938	0.983
FIBTEM MCF (mm)	−0.009	0.869	0.991	0.892	1.101

colleagues.[13] When using INR and/or aPTT above normal and/or platelet count below 100 G litre^{-1}, the authors reported an overall incidence of coagulopathy of 34% in patients with isolated head injury. On the other hand, another prospective study[14] found an above-normal INR and aPTT in 8% of patients with isolated brain injury, an incidence close to that observed in our study.

In polytrauma patients, the prevalence of prolonged standard coagulation tests and decreased platelet count was in line with that reported by others.[15] However, we observed that these patients predominantly showed low fibrinogen concentrations and impaired polymerization. Although not reported to date, this finding is not unexpected as fibrinogen is the first coagulation factor to decline during blood loss and concomitant fluid administration.[16 17] In young and middle-aged patients, such as those in the present cohort, fibrinogen concentrations are frequently at the lower end of the reference range.[18] These patients may therefore reach critical threshold values earlier than those with high initial fibrinogen levels.[19] In addition, fibrinogen serves as a substrate; it is consumed by the clotting process and is consequently needed at 1000-fold higher concentrations than other coagulation factors. Lastly, acidosis and hypothermia, frequently present in severely injured patients, aggravate the increased breakdown of fibrinogen seen during haemorrhage.[6] As recently reviewed by Fries and Martini, from a pathophysiological standpoint, fibrinogen seems of interest in many trauma patients, with the present data confirming this assumption.

In line with the European guidelines for the management of trauma patients, we defined 150 mg dl^{-1} as the critical threshold for fibrinogen. Similarly, several recent studies have reported increased blood loss in surgical patients with fibrinogen concentrations <150–200 mg dl^{-1}.[1 20–23] In addition, our clinical experience with ROTEM® assays[24 25] during the past 15 yr suggests that profuse bleeding commonly occurs at an MCF of FIBTEM<7 mm, a value that corresponds to a fibrinogen concentration of 150 mg dl^{-1}. In fact, in this study, we found that patients exhibiting values below these thresholds had a higher mortality than did those who did not. When interpreting data on fibrinogen concentrations, one should bear in mind that these measurements may relevantly overestimate fibrinogen concentrations in diluted states such as in fluid-resuscitated trauma patients. Furthermore, they delicately depend on the type of assay and thrombin reagent used.[26–28] For methodological reasons, results of prothrombin and partial thromboplastin time assays vary considerably with fibrinogen concentrations. When interpreting the here presented PT values, it should be considered that PT measurements are given as percentage of normal according to the Quick method which is commonly used in many European countries instead of measuring PT in seconds. Thus, it can be assumed that pathological low Quick values and prolonged aPTTs in some of our study patients actually reflected low fibrinogen concentrations, rather than critically decreased thrombin formation.

The incidence of a platelet count <100 G litre^{-1} was low at 4% in all study patients, but 10% and 20% of patients with isolated head injury and polytrauma, respectively, showed poor clot firmness, as shown in Figure 1. Lang and colleagues[29] demonstrated that fibrinogen profoundly impacts total clot strength independently of platelet count. Together with the observation that fibrinogen concentrations are frequently <150 mg dl^{-1}, this strongly indicates that the main mechanism responsible for reduced clot firmness in trauma patients is impaired fibrin polymerization as a

Table 5 Summary of logistic regression models (adjusted for ISS) testing the independent influence of coagulation parameters on RBC requirements during the first 6 h in polytrauma patients. PT, prothrombin time; aPTT, activated partial prothrombin time; DD, D-Dimer; EXTEM, extrinsically activated ROTEM® assay; CT, coagulation time; CFT, clot formation time; MCF, maximum clot firmness; LI60, lysis index 60 min; FIBTEM MCF, fibrin polymerization

	Regression coefficient	*P*-value	Exp (*B*)	95% CI	
PT (%)	−0.040	<0.001	0.961	0.946	0.976
aPTT (s)	0.012	0.155	1.012	0.996	1.0028
DD ratio	0.018	0.052	1.018	1.000	1.036
Fibrinogen (mg dl^{-1})	−0.006	0.003	0.994	0.991	0.998
Platelets (G $litre^{-1}$)	−0.006	0.029	0.994	0.989	0.999
EXTEM CT (s)	−0.001	0.323	0.999	0.997	1.001
EXTEM CFT (s)	0.000	0.341	1.000	0.999	1.000
EXTEM MCF (mm)	−0.21	0.198	0.979	0.947	1.011
EXTEM LI 60 (%)	0.015	0.052	1.015	1.000	1.031
FIBTEM MCF (mm)	−0.080	0.007	0.924	0.872	0.987

consequence of low fibrinogen concentrations, disturbance of polymerization, and/or increased clot lysis.

Some data show that thrombin formation is increased in trauma patients[4 5 30] because of circulating microparticles, negatively charged phospholipids and massive tissue-factor release while inhibitor levels are reduced due to blood loss and consumption. Interestingly, in this cohort study, we found that trauma patients, albeit exhibiting an increased INR and prolonged aPTT, showed substantially increased levels of prothrombin fragments and TATs, indicating maintained to increased thrombin formation. One explanation for this discrepancy could be that the INR and aPTT indicate decreased concentrations of procoagulatory factors, thereby answering the question for which these tests were developed. Nevertheless, pathological values do not necessarily indicate reduced thrombin formation in acquired coagulopathy if anticoagulatory proteins are reduced by similar amounts.[31] However, levels of AT are rarely reported for trauma patients. In fact, we found that AT values decreased concomitantly with PT, an observation previously made in bleeding orthopaedic patients during fluid administration.[24] This finding is clinically important, because liberal transfusion of FFP might unnecessarily aggravate thrombin formation and booster the inflammatory response.[32–34]

Activation of coagulation, tissue trauma, hypoperfusion, and adrenergic stress are commonly accompanied by activation of fibrinolysis, which profoundly affects clot strength. Lastly, trauma patients frequently show poor clot firmness, and weaker clots dissolve faster.[24 35] We confirm earlier reports that coagulation and fibrinolysis are similarly activated in patients with or without brain injury[30] and that clot strength and hyperfibrinolysis are factors independently affecting mortality.[9–11 36] Considering the high fatality rate for hyperfibrinolysis in our study, it seems reasonable that mortality of trauma patients can be reduced by early administration of tranexamic acid, as suggested in a recent large multicentre trial.[37] Our data showing an association between hyperfibrinolysis and hypoperfusion and also injury severity underscore the importance of avoiding hypoperfusion and the administration of antifibrinolytic therapy to severe trauma patients, especially when abdominal injuries are present.

Certain limitations of our study need to be taken into account. In comparison with retrospective studies analysing thousands of subjects, the sample size of 334 patients appears small. However, it is noteworthy that this is the so far largest prospective study simultaneously analysing both standard coagulation and ROTEM® tests in severe trauma patients.

Furthermore, in patients with multiple injuries, viscoelastic and plasmatic coagulation parameters were factors associated with early mortality and need for any red cell transfusion.

Criticism may arise from the fact that we used critical thresholds defined from our long-term clinical experience with ROTEM® assays in bleeding patients showing increased microvascular bleeding at certain values of ROTEM® parameters. However, ROC curve analysis revealed the maximum sum of sensitivity and specificity at values very close to those predefined. Nevertheless, critical thresholds for any coagulation parameter indicating increased bleeding and mortality may change with the pattern and severity of injury in the individual trauma patient. Furthermore, because treatment algorithms vary among institutions, our results may not be generally applicable.

In conclusion, ROTEM® assays reliably and differentially detected deficiencies in severe blunt trauma patients. Patients with polytrauma most frequently exhibited fibrinogen concentrations below 150 mg dl^{-1}, impaired fibrin polymerization, and poor clot firmness. These functional findings may be overlooked if trauma patients are monitored by plasmatic tests alone. Since hyperfibrinolysis was equally frequent in patients with isolated head injury and in those with polytrauma, these patients might benefit from routine ROTEM® monitoring, too. In the light of sustained or even increased thrombin formation in our trauma population, concepts using high FFP to red cell ratios seem questionable. As poor fibrin polymerization seems to be the primary reason for

weak clot firmness and weaker clots are less resistant to fibrinolysis early administration of cryoprecipitate/fibrinogen concentrates and tranexamic acid may be an attractive strategy to reduce blood loss in blunt trauma patients.[38–40] However, this hypothesis needs to be tested in future randomized trials.

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Conflict of interest

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