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Data-driven Development of ROTEM and TEG Algorithms for the Management of Trauma Hemorrhage

A Prospective Observational Multicenter Study

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Objective: Developing pragmatic data-driven algorithms for management of trauma induced coagulopathy (TIC) during trauma hemorrhage for viscoelastic hemostatic assays (VHAs).

Background: Admission data from conventional coagulation tests (CCT), rotational thrombelastometry (ROTEM) and thrombelastography (TEG) were collected prospectively at 6 European trauma centers during 2008 to 2013.

Methods: To identify significant VHA parameters capable of detecting TIC (defined as INR $>$ 1.2), hypofibrinogenemia ($<$ 2.0 g/L), and thrombocytopenia ($<$ 100 x10^9/L), univariate regression models were constructed. Area under the curve (AUC) was calculated, and threshold values for TEG and ROTEM parameters with 70% sensitivity were included in the algorithms.

Results: A total of, 2287 adult trauma patients (ROTEM: 2019 and TEG: 968) were enrolled. FIBTEM clot amplitude at 5 minutes (CA5) had the largest AUC and 10 mm detected hypofibrinogenemia with 70% sensitivity. The corresponding value for functional fibrinogen (FF) TEG maximum amplitude (MA) was 19 mm. Thrombocytopenia was similarly detected using the calculated threshold EXTEM-FIBTEM CA5 30 mm. The corresponding rTEG-FF TEG MA was 46 mm. TIC was identified by EXTEM CA5 41 mm, rTEG MA 64 mm (80% sensitivity). For hyperfibrinolysis, we examined the relationship between viscoelastic lysis parameters and clinical outcomes, with resulting threshold values of 85% for EXTEM Li30 and 10% for rTEG Ly30. Based on these analyses, we constructed algorithms for ROTEM, TEG, and CCTs to be used in addition to ratio driven transfusion and tranexamic acid.

Conclusions: We describe a systematic approach to define threshold parameters for ROTEM and TEG. These parameters were incorporated into algorithms to support data-driven adjustments of resuscitation with therapeutics, to optimize damage control resuscitation practice in trauma.

Keywords: algorithms, ROTEM, TEG, trauma hemorrhage, trauma induced coagulopathy, viscoelastic haemostatic assays

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Trauma remains one of the world's leading causes of death[1] with upwards of 2 million people dying from trauma hemorrhage each year.[1,2] Advances in our understanding of trauma-induced coagulopathy (TIC) and new approaches to resuscitation have led to large improvements in outcomes.[3] However, even in the best centers, 1 in 4 trauma patients with severe bleeding die, and overall mortality may approach 50%.[4] Current resuscitation often manages coagulopathy empirically, is nonspecific and does not correct a preexisting coagulopathy.[5,6] A targeted, precision medicine approach to the treatment of TIC may lead to improved outcomes by reducing overall requirements for red cells and component therapies.

TIC has multiple phenotypes and individual patients may present with different forms of coagulopathy at different times in their clinical course.[7,8] Contemporary resuscitation of bleeding trauma patients delivers volume resuscitation through an empiric, balanced transfusion of red blood cells, plasma, and platelets in proportions approximating that of whole blood.[9] Although this approach reduces the development of dilutional coagulopathy, it does not treat any underlying coagulopathy and does not fully support hemostasis in patients who require large volumes of transfusion.[5,6] The targeted correction of underlying coagulopathy using conventional coagulation tests (CCTs) is attractive in principle and supported by small trials.[10,11] However, the logistics of providing laboratory results in a suitable timeframe are challenging.[11,12] This has led to the suggestion of a hybrid approach, starting with empiric therapy and switching to an individualized, precision approach as soon as coagulation assessments are available.[13–15] This approach ideally requires rapidly available point of care assessments of

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coagulopathy and has resulted in renewed interest in viscoelastic hemostatic assays (VHAs) to diagnose the underlying hemostatic deficiencies and to guide coagulation support. However, there is currently insufficient data to support the use of VHAs in trauma hemorrhage.[16–20] Although a number of small studies shows VHA results can predict transfusion requirements or guide therapy, there is minimal evidence for parameters to guide the administration of coagulation therapeutics during active trauma hemorrhage.[21–23]

The overall objective of this study was to develop pragmatic data-driven algorithms for the VHAs in the management of TIC during trauma hemorrhage. Our first aim was to determine, for both thromboelastometry (ROTEM) and thromboelastography (TEG), parameters, and thresholds with high detection rate for TIC. We then aimed to determine the optimum parameters to guide therapy–specifically thresholds to guide the treatment of hypofibrinogenemia, thrombocytopenia, coagulation factor deficiency, and hyperfibrinolysis. Finally, we wished to synthesize these findings into pragmatic algorithms for clinical practice.

METHODS

Study Design

This study was part of the TACTIC (Targeted Action for Curing Trauma Induced Coagulopathy) program[24] of the International Trauma Research Network (INTRN).[25] The prospective multinational observational study ACIT (Activation of Coagulation and Inflammation in Trauma) was the research platform for the study. Patients were recruited prospectively at 6 major trauma centers in 5 different countries: the United Kingdom, Denmark, Germany, the Netherlands, and Norway.

Participants

Adult trauma patients who met the local criteria for full trauma team activation were eligible for inclusion. Patients who received more than 2000 mL of fluids before arrival in the emergency department (ED) or who arrived more than 2 hours from time of injury were excluded, as were patients who were pregnant, had known liver failure, preexisting bleeding disorders or were taking oral anticoagulants other than aspirin. Patients who had received blood products or Tranexamic Acid (TXA) before admission were not excluded. Initial consent was provided by a physician independent of the study. Written informed consent was obtained as soon as possible from the patients or their next of kin. The study was approved by local ethical authorities and performed in accordance with local ethical regulations and the Declaration of Helsinki.

Data Collection

Patient demographics, time, and mechanism of injury, prehospital fluid administration, vital signs on admission, total amount of fluids and blood products administered within the first 12 hours, and CCTs on admission were collected prospectively. Injury severity was scored when relevant information was available. TEG and ROTEM values were recorded electronically and later transferred manually to the case report form (CRF).

Sampling Techniques and Measurements

ACIT first began recruiting patients in 2008 with ROTEM, and TEG analyses were added in parallel from 2013. Blood samples were collected within 20 minutes of arrival in the ED. Samples for TEG, ROTEM, and CCTs were collected in citrated tubes. Samples for blood gas analyses were collected in heparinized syringes in accordance with local routines. TEG and ROTEM were performed within 1 hour, at 37°C by dedicated study personnel using the TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemonetics Corp., Braintree, MA) and the ROTEM Delta (TEM international GmbH, Munich, Germany). The methodology and the parameters of TEG and ROTEM have been described previously.[26,27]

ROTEM, TEG, and CCT Analyses

The ROTEM assays used in this study were the EXTEM and FIBTEM, both activated by tissue factor derived from rabbit brain, with cytochalasin D added to the FIBTEM sample for platelet inhibition.[27] TEG assays were standard TEG, where the sample is activated by Kaolin, Rapid TEG (rTEG) where the sample is activated by both Kaolin and tissue factor, and Functional Fibrinogen TEG (FF TEG) where lyophilized tissue factor with a platelet inhibitor Abciximab (a glycoprotein IIb/IIIa-inhibitor) is added for platelet inhibition to isolate the fibrin component of the clot.[27] The CCTs were Prothrombin Time (PT), fibrinogen concentration and platelet count (PLT). PT was converted to international normalized ratio (INR) in accordance with the specific reagents and device characteristics in the respective laboratories. Fibrinogen was measured by the Clauss method.[28]

Definitions

We defined the presence of TIC as INR > 1.2;[12] hypofibrinogenemia was defined as fibrinogen concentration < 2.0 g/L;[9] and thrombocytopenia as a platelet count below 100×10^9/L.[9,19] In the absence of an accepted laboratory definition of hyperfibrinolysis in trauma patients, we aimed to determine threshold values for treatment through their relationship with mortality and transfusion requirements.

Statistical Analyses

Multiple imputations were performed on all TEG and ROTEM data, to deal with the missing data. Predictive mean matching was performed and 10 imputation sets were constructed. The imputations were tested using graphical density plots where the imputed data were plotted separately from the original data and convergence was checked. The outcomes from the analyses were pooled using Rubin's rule.[29] Statistical analyses were also performed with nonimputed data, to confirm that multiple imputations had not introduced unacceptable bias.

To identify significant VHA parameters capable of identifying TIC, hypofibrinogenemia, and thrombocytopenia univariate regression models were constructed for these outcomes and areas under the curves (AUCs) were calculated. The platelet component was examined by subtracting the FIBTEM clot amplitude at 5 minutes (CA5) from the EXTEM CA5 and the FF TEG maximum amplitude (MA) from the rTEG MA. Threshold values for TEG and ROTEM parameters with sensitivities approaching 60%, 70%, 80%, and 90% were calculated with corresponding specificities, Negative predictive values (NPVs) and Positive predictive values (PPVs).

The multiple imputations and the univariate analyses were performed with R version 3.1.2. All other analyses were performed with SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, United States).

Algorithm Development

All centers in the TACTIC program have empiric replacement therapy of high-dose plasma and platelet transfusions given alongside red blood cell transfusions as the basis of their major hemorrhage protocol.[3,19,30] All centers also empirically give tranexamic acid to all patients activating the major hemorrhage protocol.[31,32] This concept of personalized hemostasis control augmenting baseline empiric therapy has been previously described as the 'Copenhagen Concept.'[13–15]

Algorithms were based on the principles that they should be able to guide hemostatic therapy, namely fibrinogen replacement, platelet transfusions, plasma procoagulant supplementation, and

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antifibrinolytic therapy. Algorithms were also to be as pragmatic and easy to follow as possible, using parameters that were not only strongly associated with underlying coagulopathy states, but also had face validity to clinicians. The key outputs of this study are the trigger thresholds for administration of coagulation therapies. We selected the earliest available parameter that provided the required information and threshold levels that were at least 70% sensitive despite potentially low specificity, as the interventions are known to carry generally acceptable risk in a life-threatening setting. Threshold values were also selected to be easier to recall if small changes (eg, rounding up or down) would not significantly alter the performance of individual parameters. For the therapies and doses associated with these thresholds, we chose best practice levels from current guidelines and evidence.

RESULTS

From August 2008 to December 2014, a total of 2287 patients were recruited to ACIT across 6 sites. ROTEM was performed in 2019 patients, whereas 968 patients had TEG assessments on admission. Patient demographics, injury characteristics, admission parameters, and outcomes were similar in both cohorts (Table 1). Overall, approximately 6.5% of the cohort was coagulopathic by INR on admission and 15% required at least 4 units of red cell transfusions in the first 12 hours.

Detection of Hypofibrinogenemia

For ROTEM, the FIBTEM CA5 reported the highest AUC for hypofibrinogenemia (0.80) (Fig. 1) (see Table, Supplemental Digital Content 1, http://links.lww.com/SLA/B431: Detection of Hypofibrinogenemia; AUCs and 95% CI). As expected, FIBTEM maximum clot firmness (MCF) also performed well with an AUC of 0.78 (Fig. 1) (see Table, Supplemental Digital Content 1, http://links.lww.com/SLA/B431: Detection of Hypofibrinogenemia; AUCs, and 95% CI). A FIBTEM CA5 threshold of 10 mm had a sensitivity of 70%, specificity of 76% and NPV of 88% for the detection of hypofibrinogenemia (Table 2).

For TEG, the rTEG MA was the best performing variable with an AUC of 0.76 (Fig. 1) (see Table, Supplemental Digital Content 1, http://links.lww.com/SLA/B431: Detection of Hypofibrinogenemia; AUCs, and 95% CI). Both FF TEG MA and Kaolin-TEG MA had AUCs of 0.72 (Fig. 1) (see Table, Supplemental Digital Content 1, http://links.lww.com/SLA/B431: Detection of Hypofibrinogenemia; AUCs, and 95% CI). An FF-TEG MA of 19 mm had a sensitivity of 70% and specificity of 59% for the detection of hypofibrinogenemia, with an NPV of 89% (Table 2).

TABLE 1. Baseline Demographics, Injury Characteristics, Admission Parameters, Transfusion Requirement and Outcomes

	ROTEM* (n = 2019)†	TEG‡ (n = 968)§
Age, yrs	41 (27–56)	43 (29–57)
Male sex, %	76	75
Blunt injury, %	85	86
ISS	13 (5–25)	13 (5–25)
% ISS > 15	44	43
HR, bpm	86 (74–105)	83 (72–100)
Systolic BP, mmHg	131 (113–150)	131 (114–3150)
BE	−1.4 (−4.0–0.6)	−1.4 (−3.9–0.4)
Lactate, mmol/L	2.0 (1.3–3.2)	2.0 (1.3–3.0)
% INR > 1.2	6.8	5.8
aPTT	25 (23–29)	26 (23–30)
Fibrinogen, g/L	2.4 (2.0–2.9)	2.6 (2.1–3.0)
% Fibrinogen < 2.0 g/L	21.3	15.8
Platelet Count (100×10^9/L)	226 (185–267)	222 (185–264)
% Platelet count < 100×10^9/L	2	1.5
% ≥ 4 RBCs in 12 hours	15.8	13
12 hours mortality, %	2.6	2.2
28 days' mortality, %	9.3	8.2

All values are median with interquartile range, except for those marked %.

aPTT indicates activated partial thromboplastin time; BE, base excess; HR, heart rate; INR, international normalized ratio; ISS, injury severity score; RBC, red blood cell; BP, blood pressure.

*For the ROTEM values the rate of missingness ranged from 2.5% for EXTEM CT to 4.3% for EXTEM Li30.

†Data from 1534 to 2019 patients per variable.

‡For the TEG values the missingness ranged from 2.8% for Fibrinogen TEG MA to 13.0% for Rapid TEG ACT.

§Data from 847 to 968 patients per variable.

Detection of Thrombocytopenia

Only 44 (2%) ROTEM patients and 17 (1.5%) TEG patients presented with low platelet counts. The EXTEM-FIBTEM CA5 had an AUC of 0.75 for identifying patients with low platelet counts and EXTEM-FIBTEM MCF performed similarly with an AUC of 0.70 (see Table, Supplemental Digital Content 2, http://links.lww.com/SLA/B431: Detection of low platelets; AUCs, and 95% CI) (see Figure, Supplemental Digital Content 3, http://links.lww.com/SLA/B431: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG, thrombocytopenia). An EXTEM-FIBTEM CA5 threshold of 30 mm had a sensitivity of 74% with a specificity of 63% and a NPV of 99% (Table 3).

For TEG the subtracting amplitude of FF TEG MA from the rTEG MA had an AUC of 0.54 (See Table, Supplemental Digital Content 2, http://links.lww.com/SLA/B431: Detection of low platelets; AUCs, and 95% CI) (See Figure, Supplemental Digital Content 3, http://links.lww.com/SLA/B431: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG, thrombocytopenia). A rTEG – FF TEG MA threshold of 45 mm had a sensitivity of 65% with a specificity of 32% and NPV of 98% (Table 3).

Detection of Hyperfibrinolysis

To identify thresholds for the detection of hyperfibrinolysis we examined the relationship between viscoelastic lysis parameters and clinical outcomes. For ROTEM maximum lysis (ML) there was a step-change in mortality in patients with a ML above 20% (ML %: ≤ 20% vs > 20%–9.5% vs 50.0%, $P < 0.001$). At 30 minutes, the ROTEM Lysis Index (LI30) parameter showed a similar mortality outcome threshold at 85% (LI30: < 85% vs ≥ 85%–76.2% vs 10.8%, $P < 0.001$). Only 3.5% of those with an LI30 above 85% subsequently developed an ML > 20%, of which 4 patients died (10.5% mortality - not significantly different from LI30 ≥ 85% or ML < 20% groups). Mean 24-hour packed red blood cell (PRBC) requirements also increased markedly at LI30 levels below 85% (LI30: < 85% vs ≥ 85%–14 vs 7 units, $P < 0.001$).

For TEG detection of hyperfibrinolysis, there was an increase in mortality at rTEG clot lysis at 30 minutes (LY30) values above 10% (LY30: ≤ 10% vs > 10%−8.8% vs 60.0%, $P < 0.001$). There was an associated increase in PRBC requirements at this threshold: (LY30: ≤ 10% vs >10%- 2 vs 10 units, $P < 0.001$).

Detection of Coagulopathy

For ROTEM, EXTEM CA5 had the greatest AUC (0.78) for identification of INR >1.2, which was closely followed by the MCF, clot formation time (CFT), α-angle and clotting time (CT) (0.76, 0.76, 0.75, and 0.72, respectively) (Fig. 2) (See Table, Supplemental Digital Content 4, http://links.lww.com/SLA/B431: Detection of Coagulopathy; AUCs and 95% CI). A CA5 threshold of 41 mm

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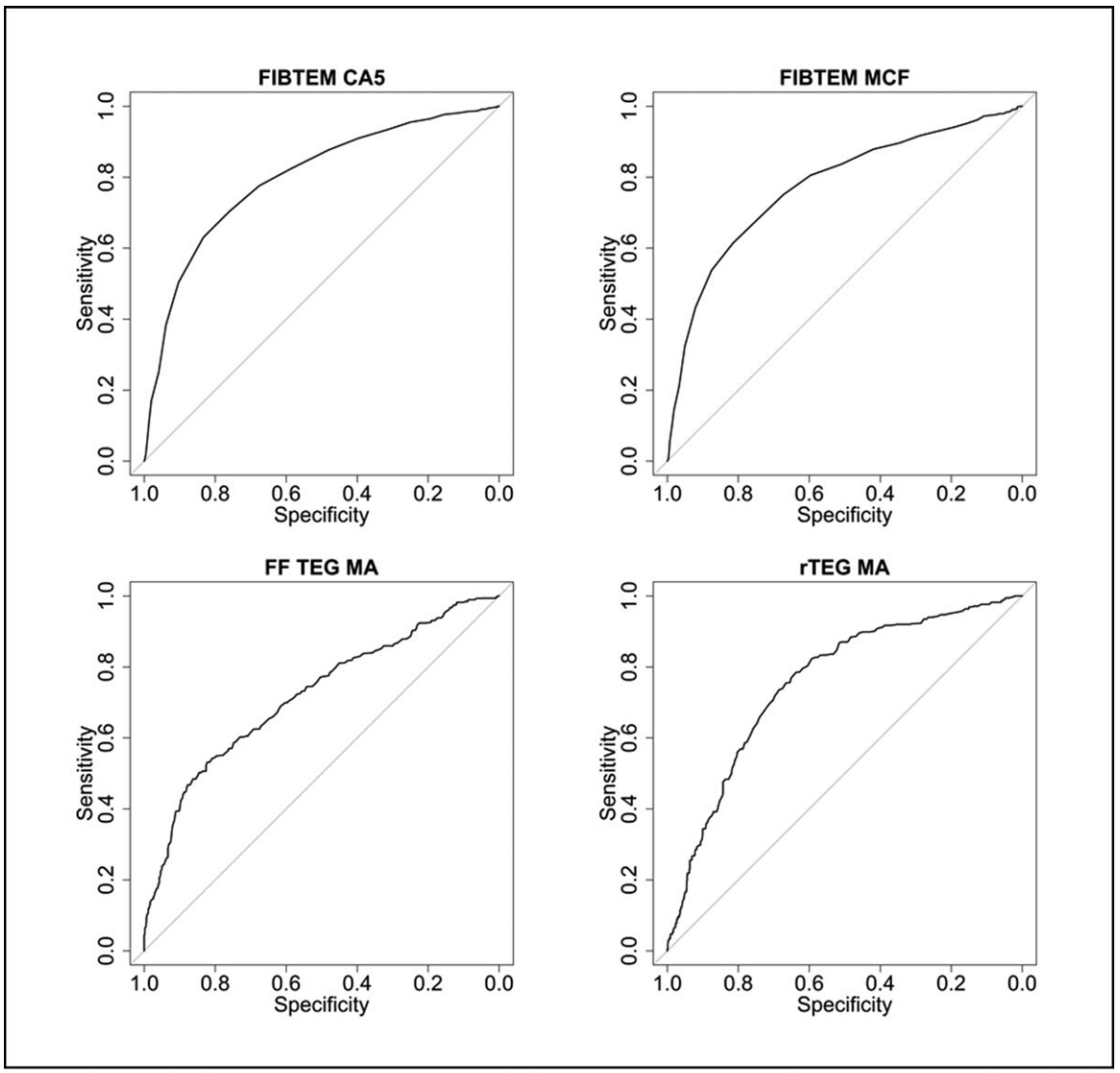


FIGURE 1. Receiver operator characteristic (ROC) curves, ROTEM and TEG, hypofibrinogenemia (fibrinogen < 2.0 g/L).

had a sensitivity of 73% for the detection of coagulopathy with a specificity of 70%, and a NPV of 97% (Table 4).

For detection of coagulopathy with TEG the highest AUC was with the FF TEG reaction time (r), α-angle and MA parameters, all with an AUC of 0.73 (Fig. 2) (See Table, Supplemental Digital Content 4, http://links.lww.com/SLA/B431: Detection of Coagulopathy; AUCs, and 95% CI). The rTEG r performed similarly with an AUC of 0.71, with rTEG activated clotting time (ACT) and MA at 0.69 and 0.67 respectively (Fig. 2) (See Table, Supplemental Digital Content 4, http://links.lww.com/SLA/B431: Detection of Coagulopathy; AUCs, and 95% CI). The best performing Kaolin-TEG variable was the MA with an AUC of 0.71. The Kaolin-TEG r had a much lower AUC at 0.58 (See Table, Supplemental Digital Content 4, http://links.lww.com/SLA/B431: Detection of Coagulopathy; AUCs, and 95% CI). An rTEG ACT of 121 had a sensitivity of 63% for detection of coagulopathy with a specificity of 68% and a NPV of 96% (Table 4).

Algorithm Development

Based on the analyses above, we constructed management algorithms for ROTEM, TEG, and CCTs (Fig. 3A–C respectively) to be used in addition to baseline damage control resuscitation (empiric high-dose plasma and platelets and baseline administration of tranexamic acid).

ROTEM

Given the principles of timely availability, adequate performance, and pragmatic triggers, we defined a FIBTEM CA5 threshold of 10 mm for the dosing of additional fibrinogen (Table 2). For administering additional platelets transfusions, we used the EXTEM

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TABLE 2. Detection of Hypofibrinogenemia (Fibrinogen < 2.0 g/L)

	Parameter	Threshold, mm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ROTEM						
FIBTEM	CA5	9	63	83	58	86
AUC: 0.80		**10**	**70**	**76**	**51**	**88**
		12	82	59	42	90
		14	91	40	35	92
FIBTEM	MCF	11	62	81	54	85
AUC: 0.78		13	75	67	45	88
		14	81	60	42	90
		18	92	29	32	91
TEG						
Rapid TEG	MA	59	60	77	39	89
AUC: 0.76		60	70	71	37	91
		62	80	60	33	93
		64	90	42	28	94
FF TEG	MA	18	60	73	36	88
AUC: 0.72		**19**	**70**	**59**	**30**	**89**
		21	81	45	27	91
		24	90	24	23	91

AUC indicates area under the curve; CA5 , clot amplitude at 5 minutes; FF, functional fibrinogen; MA, maximum amplitude; MCF, maximum clot firmness; NPV, negative predictive value; PPV , positive predictive value.
Bold: closest calculated value to chosen threshold for algorithms.

CA5 – FIBTEM CA5 threshold of < 30 mm. To identify those patients who may require additional plasma despite sufficient replacement of fibrinogen and platelets we selected a standard EXTEM CT value of > 80 seconds in the presence of a noncoagulopathic EXTEM CA5 (> 40 mm). Additional TXA would be administered when EXTEM LI30 < 85%.

TEG

We constructed a TEG algorithm using the same principles. We selected a FF TEG < 20 mm as a threshold value for additional fibrinogen (Table 2). For other parameters, rTEG parameters were used rather than Kaolin TEG for their timeliness,[33] given there was no significant loss of sensitivity or specificity across these tests. We chose a rTEG – FF TEG MA below 45 mm as a threshold for giving additional platelet transfusions (Table 3). For additional plasma, we again used a standard rTEG ACT > 120 seconds' threshold provided there was no indication for fibrinogen or platelets [ie, rapid TEG MA > 65 mm (Table 4)]. A Rapid TEG LY30 > 10% was used as a threshold value for additional TXA.

For both ROTEM and TEG algorithms, the suggested therapeutic interventions are the same and based on current best practice guidance or evidence. For fibrinogen supplementation, we suggest a replacement dose of 4 g (usually as cryoprecipitate or fibrinogen concentrate)[34]; for low platelet levels, we suggest 1 pool of platelet transfusions; for evidence of low procoagulant activity, we suggest additional plasma as an extra 4 units of FFP[6]; and for evidence of hyperfibrinolysis, we suggest an additional 1 g bolus of tranexamic acid.[35,36]

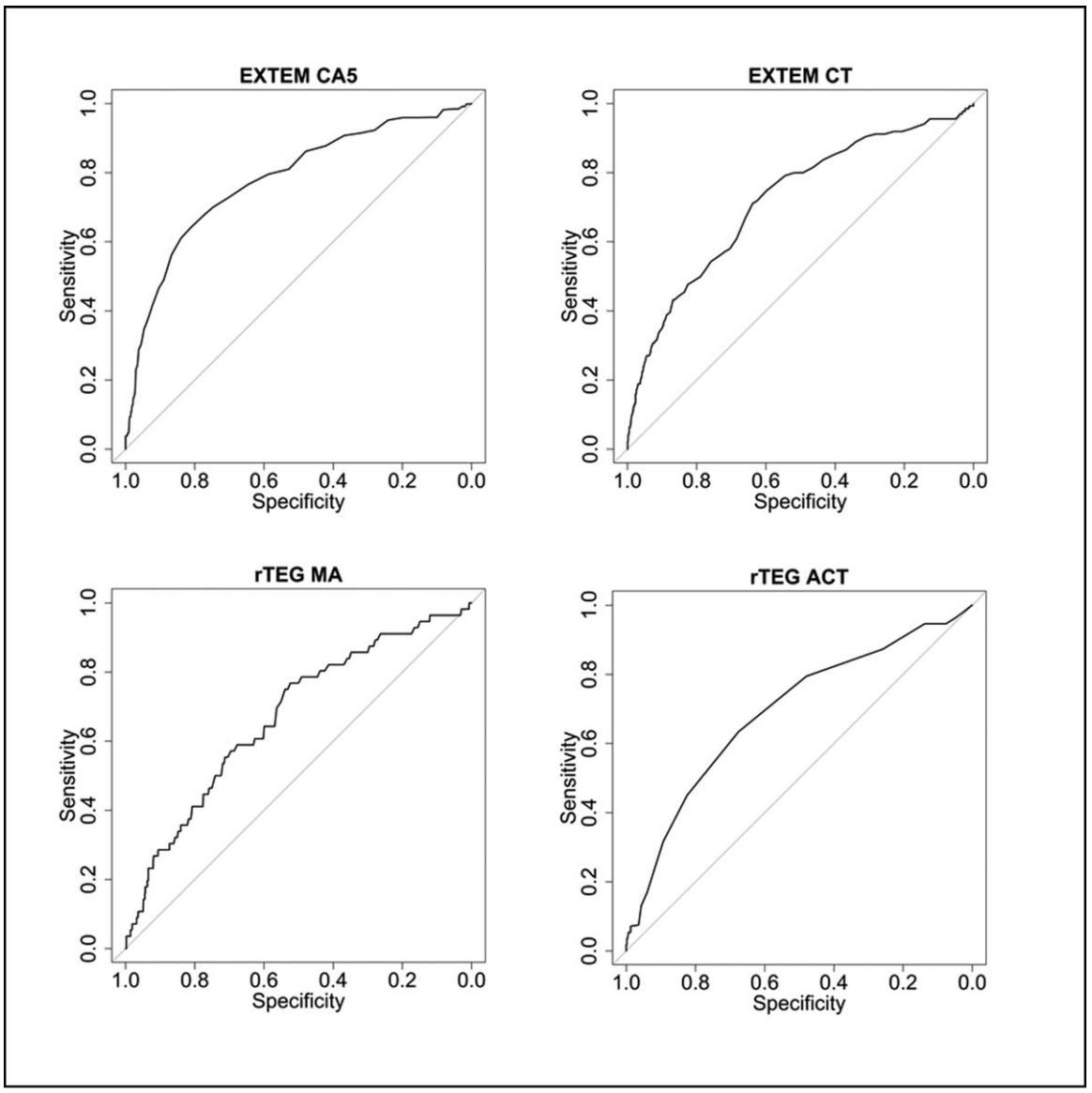
TABLE 3. Detection of Thrombocytopenia (platelet count < 100×10^9/L)

	Parameter	Threshold, mm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ROTEM						
EXTEM – FIBTEM	CA5	27	62	80	6	99
AUC: 0.75		**30**	**74**	**63**	**4**	**99**
		32	83	47	3	99
		35	91	24	3	99
EXTEM – FIBTEM	MCF	44	62	74	5	99
AUC: 0.70		47	74	53	3	99
		49	84	34	2	99
		51	90	18	2	99
TEG						
Rapid-TEG – FF TEG	MA	**45**	**65**	**32**	**2**	**98**
AUC: 0.54		46	75	21	2	98
		48	84	13	2	98
		50	92	7	2	98

AUC indicates area under the curve; CA5, clot amplitude at 5 minutes; FF, functional fibrinogen; MA, maximum amplitude; MCF, maximum clot firmness; NPV, negative predictive value; PPV, positive predictive value.
Bold: closest calculated value to chosen threshold for algorithms.

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CA5= Clot Amplitude at 5 minutes, CT= Clotting Time, rTEG= rapid TEG, MA= Maximal Amplitude, ACT= Activated Clotting Time

FIGURE 2. Receiver operator characteristic (ROC) curves, ROTEM and TEG, coagulopathy (INR $>$ 1.2).

DISCUSSION

We have defined accurate, rapidly available parameters that identify the key coagulation derangements that are corrected by available therapeutics, together with threshold values for their administration. With this large prospective cohort study across 5 countries we have developed data-driven algorithms for individualized hemostasis management of trauma patients. We adopted a pragmatic approach focusing on available hemostatic therapies as an addition to baseline damage control resuscitation. The empiric ratio MTP continues until hemostasis, adding the available hemostatic therapies as guided by TEG/ROTEM or CCT as soon as the test results are available. In studying ROTEM and TEG devices in parallel, we have produced algorithms applicable to all centers regardless of which device is available. This study therefore fills a considerable evidence gap in the role of viscoelastic hemostatic assays in the management of bleeding trauma patients.[16–18,20,21]

The parameters proposed in this study will need further validation in subsequent studies. For internal validation, the ACIT study continues to run across the INTRN sites. External validation will be needed from other centers and networks, especially those in other countries and healthcare systems. Although the parameters and thresholds used in our algorithms were data driven, there was limited evidence for the choice or dose of therapeutic agents. We used a combination of available evidence, guidelines, and intrinsic expertise alongside the desire for the algorithms to be broadly applicable at an international level. Each individual agent and dose is worthy of further study. As a whole, the algorithms are being taken forward by

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TABLE 4. Detection of Coagulopathy (INR > 1.2)

	Parameter	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ROTEM						
EXTEM	CA5	37 mm	61	84	24	96
AUC: 0.78		**41 mm**	**73**	**70**	**16**	**97**
		44 mm	81	53	12	97
		47 mm	91	37	10	98
EXTEM	CT	66 s	61	68	13	96
AUC: 0.72		64 s	71	64	14	96
		58 s	80	49	11	97
		52 s	90	31	10	98
TEG						
Rapid TEG	MA	51 mm	61	63	10	96
AUC: 0.67		62 mm	71	55	10	97
		64 mm	**80**	**44**	**9**	**97**
		66 mm	91	26	8	98
Rapid TEG	ACT	**121 s**	**63**	**68**	**12**	**96**
AUC: 0.69		113 s	80	48	9	97
		105 s	87	26	7	97
		97 s	95	14	7	98

ACT indicates activated clotting time; AUC, area under curve; CA5, clot amplitude at 5 minutes; CT, clotting time; MA, maximum amplitude; NPV, negative predictive value; PPV, positive predictive value.
Bold: closest calculated value to chosen threshold for algorithms

the TACTIC partners into a randomized controlled trial (RCT) of viscoelastic assays versus conventional coagulation therapy (the iTACTIC trial, ClinicalTrials.gov Identifier: NCT02593877). This should provide evidence for the whole algorithm approach, which can be refined and updated with future investigations.

There are several limitations to our study in addition to the lack of a separate validation set. Despite the large cohorts and high injury severity scores, the number of coagulopathic and massively bleeding patients was around 15%. Some specific derangements, such as low platelet counts, were very rare, especially as we focused on the first sample drawn after admission. This will lead to bias to the negative predictive value of a parameter and potentially underrepresent their positive predictive value and overall accuracy. Thresholds for hyperfibrinolysis had to be determined from clinical correlates in the absence of a definitive laboratory comparator test. The prehospital use of tranexamic acid will have contributed to the relatively low observed rates of admission hyperfibrinolysis, but should not have affected the actual threshold levels we calculated. Further external validation studies should be performed to confirm the applicability of these criteria for antifibrinolytic administration.

Some of the differences in performance between ROTEM and TEG parameters are also likely to be due to the difference in sample sizes between the 23 cohorts. As we aimed to develop internationally relevant algorithms, we did not explore between-center variations in prehospital or inhospital practices. However, overall the clinical and transfusion practices at the centers are more similar than they are

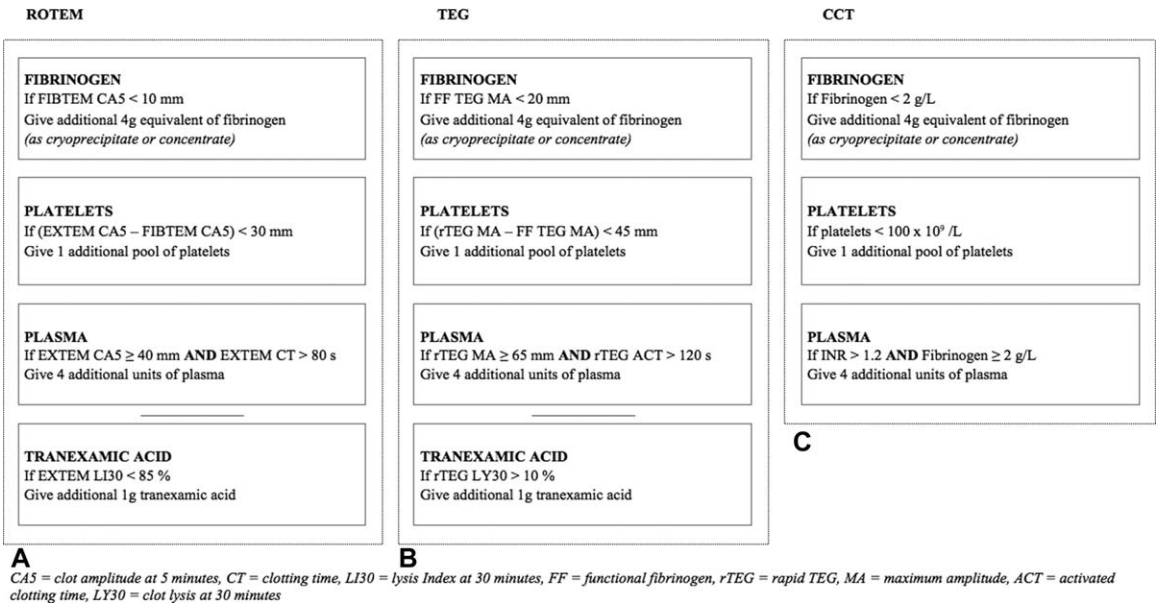


FIGURE 3. Algorithms.

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different, and all adhere to modern practices of damage control resuscitation.[30] We therefore believe the study findings represent the real-world situation and are thus broadly applicable across similar healthcare systems.

CONCLUSIONS

In this large prospective cohort study, we have determined the clinically optimal tests, parameters and thresholds to guide hemostatic therapies in trauma patients. We present algorithms for a precision approach to TIC, augmenting standard damage control resuscitation practice. These algorithms are being taken forward for evaluation in the iTACTIC multicenter randomized controlled trial of viscoelastic assays versus CCTs on clinical outcomes in trauma hemorrhage.

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