The coagulopathy underlying rotational thromboelastometry derangements in trauma patients: a prospective observational multicenter study

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Abstract

Background: Viscoelastic hemostatic assays such as rotational thromboelastometry (ROTEM®) are used to guide treatment of trauma induced coagulopathy. We hypothesized that ROTEM derangements reflect specific coagulation factor deficiencies after trauma.

Methods: Secondary analysis of a prospective cohort study in six European trauma centers in patients presenting with full trauma team activation. Patients with dilutional coagulopathy and patients on anticoagulants were excluded. Blood was drawn on arrival for measurement of ROTEM®, coagulation factor levels and markers of fibrinolysis. ROTEM® cut-off values to define hypocoagulability were: EXTEM clotting time (CT) >80s, EXTEM clot amplitude after 5 minutes (CA5) <40mm, EXTEM lysis at 30 minutes (Li30) <85%, FIBTEM clot amplitude after 5 minutes (CA5) <10mm and FIBTEM lysis at 30 minutes (Li30) <85%. Based on these, patients were divided into 7 deranged ROTEM® profiles and compared to the reference group (ROTEM® values within reference range). The primary endpoint was coagulation factors levels and fibrinolysis.

Results: Of 1828 patients, 40% had ROTEM® derangements 40.0%, most often consisting of a combined decrease in EXTEM and FIBTEM CA5, that was present in 217 (11.9%) patients. While an isolated EXTEM CT>80s had no impact on mortality, all other ROTEM® derangements were associated with increased mortality. Also, coagulation factor levels in this group were similar to patients with a normal ROTEM®. Of coagulation factors, decrease was most apparent for fibrinogen (with a nadir of 0.78 g/L) and for factor V levels (with a nadir of 22.8%). In addition, increased fibrinolysis can be present when LI30 is normal but EXTEM and FIBTEM CA5 is decreased

Conclusion: Coagulation factor levels and mortality in the group with an isolated clotting time prolongation is similar to patients with a normal ROTEM®. Other ROTEM® derangements are associated with mortality and reflect a depletion of fibrinogen and factor V. Increased fibrinolysis can be present when lysis after 30 minutes is normal.

Introduction

Trauma is a leading cause of mortality, with at least a quarter of deaths attributable to hemorrhage[1-3]. As a result, uncontrolled bleeding is the most common cause of preventable death in trauma patients[4]. Up to one third of bleeding patients develops trauma induced coagulopathy, which enhances bleeding and is associated with increased transfusion requirements, organ failure and mortality[5]. Trauma induced coagulopathy occurs due to a combination of tissue injury and shock and is characterized by hemostatic abnormalities that include fibrinogen depletion, inadequate thrombin generation, platelet dysfunction and dysregulated fibrinolysis[4, 5]. In order to improve outcome, a precision approach to correct coagulopathy while avoiding unnecessary transfusions seems key. In this regard, the potential of viscoelastic hemostatic assays to monitor the coagulation status of trauma patients is increasingly studied due to the comprehensive information provided by these assays. Viscoelastic hemostatic assays, such as rotational thromboelastometry (ROTEM®) are point of care coagulation tests in whole blood with the ability to rapidly assess the full scope of the coagulation cascade and provide parameters that reflect in vitro initiation of coagulation, clot propagation and fibrinolysis[6-8].

Currently, both conventional coagulation tests such as platelet count, prothrombin time , activated partial thromboplastin time as well as viscoelastic testing are used to guide treatment of trauma induced coagulopathy. Studies show a possible advantage of the use of viscoelastic testing to monitor trauma induced coagulopathy[9-13], at least in the subset of patients with brain injury[14]. Importantly, the currently used ROTEM® based treatment algorithms are constructed based on need for transfusion instead of on coagulation deficiencies. Thereby, the specific coagulation deficiencies underlying ROTEM® derangements used in these algorithms remain unknown. This study aims to investigate the relation between deranged ROTEM® profiles, coagulation factor levels and markers of fibrinolysis in trauma patients. We hypothesized that ROTEM® derangements have the potential to reflect specific in vivo coagulation deficiencies that are clinically relevant and are associated with adverse outcome. Results can improve the understanding of the meaning of ROTEM® derangements in a trauma setting.

Methods

Study design and participants

This study is conducted as part of a prospective multicentre trial, termed Activation of Coagulation and Inflammation in Trauma (United Kingdom Clinical Research Network Study Portfolio, ID: 5637). The Activation of Coagulation and Inflammation in Trauma study is a long-term observational cohort study that investigates early changes in coagulation and inflammation after trauma, performed in six European level-1 trauma centers in London, Oslo, Copenhagen, Oxford, Cologne and Amsterdam. For the analysis of this subset of patients, samples collected between January 2008 and November 2016 were used. Patients ≥ 18 years admitted with a full trauma team activation and that arrived within two hours after injury were screened for inclusion. Patients were not eligible if they received > 2L of clear intravenous fluids before hospital admission in order to exclude patients with a dilutional coagulopathy and capture patients with trauma induced coagulopathy , suffered from burns covering > 5% of the body or if they had known liver failure, were taking anticoagulant medication other than aspirin or had pre-existing bleeding disorders. Furthermore, patients were excluded for data analysis if there were no EXTEM plus FIBTEM ROTEM® variables available. This study was performed in accordance with the Statement of the Declaration of Helsinki and conducted after approval by the East London and The City Research Ethics Committee (07/Q0603/29) and the national ethics committees of participating centers. Written informed consent was obtained from each patient or from a legal representative in the case of incapacitated patients.

Data collection

Data was collected to a centralized database and included patient demographics, mode of injury, injury severity score, vital signs and laboratory test results at admission as well as 12 hours and 28-day mortality. In addition, the amount of fluids as well as amount of transfusions of red blood cells, fresh frozen plasma and platelet units received between time of injury and baseline sampling at the emergency department were collected.

Blood samples were drawn in citrated tubes upon emergency department arrival. After blood samples were drawn, ROTEM® was performed within 1 hour at 37°C by trained study personnel on the ROTEM® Delta (TEM™ international GmbH, Munich, Germany). Intrarater and interrater variability of this test have previously been published[15].

Coagulation markers

Samples were analysed with an automated analyser (Sysmex CA-CS2100i System, Siemens, AG, Germany) to measure coagulation factor activity [normal range]: II [78 – 117%], V [66 – 114%], VII [50 – 150%], VIII [50 – 150%], IX [58 – 138%], X [50 – 150%] and XIII [70 – 140%] with intra and inter assay coefficients of variation below 5%[16]. Clauss fibrinogen was processed by the central hospital laboratory. Enzyme linked immunosorbent essays were used to quantify levels of D-dimer, alpha 2-antiplasmin, plasmin antiplasmin complexes and tissue plasminogen activator. Coagulation assays have been performed batchwise and without previous freeze thaw cycles, thereby decreasing inter-test variability.

Definitions of hypocoagulability

In this study, both the EXTEM and FIBTEM tracings of ROTEM® are used. In the EXTEM tracing, coagulation is activated by tissue factor derived from rabbit brain. In the FIBTEM tracing, coagulation is also activated by tissue factor with the addition of cytochalasin D to inhibit platelet function in order to assess the effect of fibrinogen on clot formation. These tracings were chosen since EXTEM and FIBTEM derangements are relevant and frequent issues in trauma induced coagulopathy. Furthermore, FIBTEM is more sensitive to fibrinolysis compared to EXTEM [17-19]. The following ROTEM® cut-off values were used to define hypocoagulability EXTEM clotting time (CT) >80s, EXTEM clotting amplitude at 5 minutes (CA5) <40mm, EXTEM lysis index at 30 minutes (Li30) <85%, FIBTEM CA5<10mm and FIBTEM Li30<85%. The cut-off value for CT was chosen based on the recommendation by a consensus group on viscoelastic test-based transfusion guidelines for early trauma resuscitation as well as the ROTEM® reference value, since current evidence is insufficient to

recommend an exact CT threshold for transfusion[20]. The choice for the CA5 and Li30 thresholds was based on previous work in this same patient cohort which demonstrated that these thresholds have a good performance to predict transfusion requirement or mortality[21].

For the analyses, patients were categorized into eight groups based on admission ROTEM® profiles. Group 1: patients with a normal ROTEM®. Group 2: patients with an isolated EXTEM CT prolongation (EXTEM CT>80s). Group 3: patients with a decrease in EXTEM CA5 (EXTEM CA5<40mm). Group 4: patients with a decrease in FIBTEM CA5 (FIBTEM CA5<10mm). Group 5: patients with a normal EXTEM CT (≤80s) but with a decreased EXTEM and FIBTEM CA5 (EXTEM CA5<40 and FIBTEM CA5<10). Group 6: patients with a prolonged EXTEM CT, decreased EXTEM CA5 and decreased FIBTEM CA5 (EXTEM CT≤80s, EXTEM CA5<40mm and EXTEM CA5<10mm). Group 7: patients with a normal EXTEM CT, but with decreased EXTEM and FIBTEM CA5 in combination with Li30 <85 in either the EXTEM or FIBTEM tracing (EXTEM CT≤80s, EXTEM CA5<40mm, FIBTEM CA5<10mm, EXTEM Li30 or FIBTEM Li30 < 85%). Group 8: patients with a prolonged EXTEM CT, decreased EXTEM and FIBTEM CA5 and Li30<85% in either the EXTEM or FIBTEM tracing (EXTEM CT>80s, EXTEM CA5<40mm, FIBTEM CA5<10mm, EXTEM or FIBTEM Li30<85%).

Statistical analysis

A data analysis and statistical plan was performed as part of a secondary analysis of the Activation of Coagulation and Inflammation in Trauma study and therefore the sample size of this descriptive observational cohort study was based on the available data and no a priori statistical power calculation was conducted. A statistical analysis plan was made prior to accessing the data. No minimum clinically meaningful effect size was defined prior to data access. Previous analyses of this cohort have been used to construct a ROTEM® based treatment algorithm for trauma induced coagulopathy, related to clinical outcome [21]. Data is presented as median with interquartile range for numerical variables and as percentages for categorical variables. ROTEM® profile group is the independent variable with levels of coagulation factors and fibrinolysis markers as dependent variable. Levels of coagulation

factors and fibrinolysis markers were the primary outcome and mortality was the secondary outcome. Statistical significance between the previously defined groups was computed using a Kruskall Wallis test with Bonferroni correction for multiple testing with pairwise comparison with a Mann-Whitney U test. Categorical variables were compared with a Chi-square test. A two-tailed p-value <0.05 was considered statistically significant. Missing data was likely at random as they appeared in all participating centres and across all injury severity scores and not imputed, although this study in severely injured trauma patients carries a risk for selection bias. Furthermore, in response to peer review, an adjusted association between mortality and ROTEM derangement was added as a post hoc sensitivity model, which can be found in the supplements. To do this, a binary logistic regression was performed to correct for age, sex, lactate as a marker for shock and injury severity as possible confounders for mortality. This resulted in a model with mortality as outcome variable and age, sex, lactate, injury severity score and ROTEM derangement group as predictor variables. These predictor variables were selected based on their clinical association with mortality after trauma. Statistical analysis was performed with SPSS version 26.0 (IBM, New York City, New York, the United States) and graphs were made with Graphpad version 9.1.0 (San Diego, California, the United States).

Results

Of 1855 eligible patients, 27 patients could not be stratified into one of the eight predefined subgroups, leaving 1828 patients for analysis (baseline demographics in Table 1). Tranexamic acid was administered in hospital as part of the major hemorrhage protocol and 105 patients (5.7%) received tranexamic acid prior to baseline sampling. A deranged ROTEM® profile was present in 732 patients (40%) patients and most often consisted of a combined decrease in EXTEM and FIBTEM CA5 present in 217 patients (11.9%). On the other hand, hyperfibrinolysis (Li30<85% in either EXTEM or FIBTEM tracing) was observed only in 35 patients (1.9%). Injury severity score was higher in patients with a combination of ROTEM® derangements and was the highest when all parameters were deranged. Moreover, patients with a derangement in all ROTEM® parameters were most in shock. When compared to the other groups, platelet count was most markedly decreased in the group where all ROTEM® parameters were deranged, although the median level remained above $150x10^9$/L. Furthermore, this group was the only one with an increase in prothrombin time and activated partial thromboplastin time above reference range.

The relation between ROTEM® profiles and coagulation factor levels

In patients with an isolated CT>80s, none of the factor levels were lower when compared to patients with a normal ROTEM® (Figure 1). In patients with an EXTEM CA5<40mm, fibrinogen was the only factor level that was decreased compared to patients with a normal ROTEM®, whereas in patients with a FIBTEM CA5<10mm, fibrinogen as well as coagulation factors II, V and XIII were decreased compared to patients with a normal ROTEM®. In all other ROTEM® coagulation groups, coagulation factors I (fibrinogen), II, V, VII, IX, X and XIII displayed a similar pattern of gradual decrease as more ROTEM® parameters became deranged. Of these, fibrinogen and factor V but not the other factors, decreased below 50%. Patients with a combined CT>80s, EXTEM CA5<40mm and FIBTEM CA5<10mm derangement had a median value of factor V of 38.3% (25.0 – 71.6%) and patients with a combination of all ROTEM®

derangements (CT, EXTEM and FIBTEM CA5 and Li30) had the most severe factor V depletion of 22.8% (8.9 – 33.5%).

The relation between ROTEM® profiles and levels of fibrinolysis markers

Compared to patients with a normal ROTEM®, a finding of EXTEM or FIBTEM Li30<85% was associated with increased levels of D-dimer (78681 ng/mL vs. 6658 ng/mL), plasmin antiplasmin complexes (21587 µg/L vs. 2753 µg/L) and a decreased level of alpha 2-antiplasmin (32.1 pg/mL vs. 98.9 pg/mL), thus indicating fibrinolysis (Figure 2). Increased fibrinolysis as reflected by a Li30<85% was often accompanied by other ROTEM® derangements. Of importance, fibrinolysis was also present in the groups with deranged CT or CA5 but with a normal Li30. The group with a LI30 derangement without EXTEM CT prolongation was small with a high variability in levels of fibrinolysis markers, resulting in an absence of statistical significance compared to the group with a normal ROTEM®.

The relation between ROTEM® derangements and outcome

Patients with a deranged ROTEM® profile received more red blood cell transfusion after hospital admission and had a higher mortality compared to patients with a ROTEM® profile within reference range. Mortality was highest when fibrinolysis or multiple ROTEM® derangements were present. Furthermore, ROTEM profiles remained significantly associated with mortality after correction for confounders (p=0.009, supplemental table 3). An exception to this finding were the patients with an isolated CT prolongation, in whom outcome was comparable to patients that present with a normal ROTEM®.

Discussion

There is a surge of attention to the use of ROTEM® in trauma management. This study aims to improve understanding of the coagulopathies that are reflected by ROTEM® derangements. We report the following clinically relevant findings: 1) In the group with an isolated CT prolongation, levels of coagulation factors as well as outcome were similar to patients with a normal ROTEM®, 2) in patients with a deranged ROTEM®, levels of fibrinogen and factor V show the most pronounced decrease, 3) FIBTEM CA5 derangements reflect more severe coagulation factor deficiencies than EXTEM CA5 derangements, 4) lastly, fibrinolysis also occurs when EXTEM and FIBTEM CA5 are both deranged in the presence of a normal Li30.

An isolated EXTEM CT prolongation is thought to reflect abnormalities in clot initiation in the tissue factor dependent coagulation pathway, in particular deficiencies of coagulation factor I (fibrinogen), II, V and VII[22]. Therefore, it has been suggested that CT derangements may reflect the need for plasma (or coagulation factor concentrate). In line with this, current trauma guidelines advise that a CT prolongation may be considered an indication for plasma transfusion but that current evidence thus far is insufficient to recommend specific thresholds. [20, 23]. Our data show that the hemostasis profile of patients with an isolated CT prolongation is similar to patients that present with a normal ROTEM® profile. Of importance, an isolated EXTEM CT>80s was not related to adverse outcome. Therefore, we suggest that an isolated EXTEM CT>80s is not the appropriate cut-off level that should trigger plasma or coagulation factor concentrates, because many patients will have adequate coagulation factor levels. This gives rise to the question whether an alternative CT cut off value would provide a better positive predictive value for coagulation disturbance. However, the clinical relevance of this question is debatable considering that in our cohort, none of the patients with an isolated CT prolongation died. This suggests that clinically relevant CT prolongations are accompanied by other ROTEM® derangements and a CT prolongation in combination with other ROTEM® abnormalities should trigger plasma transfusion. Of note, a CT prolongation can also reflect anticoagulant treatment [24-26]. Since these patients were excluded in this study, our results are not generalizable to patients on oral anticoagulants other than aspirin.

Despite increasing evidence on the association between coagulation factor depletion, trauma induced coagulopathy and adverse outcome, it is not known which activity of factor levels is optimal after trauma[27, 28]. Although it is assumed that normal hemostasis requires a coagulation factor activity between 20 – 50%, these levels are based on patients with a single factor deficiency[29]. The clinical importance of a more modest but simultaneous decrease in activity of several coagulation factors should probably not be underestimated and may also contribute to trauma induced coagulopathy [30]. However, our results suggest differential decreases in factor levels as demonstrated already for cardiac surgery[31]. In spite of a gradual decrease as more ROTEM® parameters become deranged, levels of coagulation factor II, VII, VIII, IX, X and XIII remain largely within normal range, even in groups with increased mortality. In contrast, levels of fibrinogen and factor V decrease more frequently and more severely after injury. Given the association between fibrinogen levels and mortality, it is recommended to maintain levels of fibrinogen above 1.5 g/L[23, 32]. In our cohort, a combination of ROTEM® EXTEM and FIBTEM CA5 derangements represents a fibrinogen depletion < 1.5 g/L and should trigger fibrinogen suppletion. Of interest, factor V depletion in our cohort equaled that of fibrinogen. This finding is consistent with previous studies showing a marked decrease in factor V, while other factor levels remained relatively normal[30, 33]. In particular factor VII does not decrease. We offer the following explanation for these findings: in trauma induced coagulopathy, activated Protein C is increased which inhibits factor V and VIII with ensuing factor X, and fibrinogen, whereas factor VII remains out of this activation loop. Of note, a decrease in factor V activity in our study is associated with increased mortality[34]. This begs the question whether substitution of factor V in severely injured patients is rational. It is important to consider that factor V is not present in the currently trialed 4 factor concentrates (NCT04534751).

A decreased FIBTEM CA5 reflects more severe depletion of fibrinogen and factor levels than EXTEM CA5, as found before[35, 36]. This finding may beg the question whether the dosage of

substitution of factor levels should be higher in case of low FIBTEMCA5 compared to low EXTEMCA5.

Hyperfibrinolysis as measured with viscoelastic testing is a relevant finding, associated with increased mortality and massive transfusion, with incidences reported as high as 32.5% based on FIBTEM LI60 < 85% [7, 37, 38]. In our cohort, hyperfibrinolysis measured by Li30 is rare. This is not unexpected given the low sensitivity of Li30. Of note, EXTEMLi60 and even better FIBTEM Li60 are more sensitive to detect moderate to mild hyperfibrinolysis[7, 8, 39]. However, the detection time for Li60 is long and untreated fibrinolysis can aggravate bleeding. Therefore, early diagnosis of fibrinolysis with Li30 is used in clinical ROTEM® algorithms[14].

An important finding, is that a combination of CT and CA5 derangements also reflects increased fibrinolysis, even when Li30 was normal. A retrospective study in patients undergoing non cardiac surgery was able to demonstrate that low early values of clot firmness in the EXTEM pathway are associated with fibrinolysis[40]. Accordingly, our results demonstrate that in trauma patients, a combination of EXTEM and FIBTEM CA5 derangements represent increased D-dimer with a concomitant decrease in alpha 2 antiplasmin, indicating fibrinolysis. Furthermore, when EXTEM and FIBTEM CA5 derangements are accompanied by CT prolongation, fibrinolysis becomes even more outspoken. This indicates that elevated fibrinolysis should not be ruled out in these patients and that combined ROTEM® derangements should trigger (repeated) antifibrinolytic therapy.

This study has limitations. Patients with a dilutional coagulopathy and patients on anticoagulant treatment were excluded and we therefore cannot make recommendations about these patient categories. In addition, the study was performed some time ago. Since then, prehospital interventions such as administration of tranexamic acid have become more common. However, we do not think that this influences the implications of our findings, as a deranged ROTEM® should trigger an intervention regardless of previously administered therapy. Moreover, we cannot rule out selection bias as families of the most severely injured patients are less likely to give consent, possibly leading to smaller samples in the more deranged

ROTEM® groups. Furthermore, EXTEM and FIBTEM LI60 results are not available in this study which resulted in the low incidence of reported hyperfibrinolysis based on ROTEM results. Lastly, general limitations of ROTEM® should be acknowledged. ROTEM® measurements are not sensitive to the effect of platelet inhibitors nor the effect of Von Willebrand Factor on clot formation, which is particularly relevant in patients with severe injury since Von Willebrand Factor can be released by the endothelium as a response to severe trauma.

Our findings are relevant, as the ROTEM derangements appear to be independently associated with outcome. Results enable potential improvement of trauma induced coagulopathy treatment when bleeding is deemed clinically relevant. We propose to adjust ROTEM® based algorithms by omitting an isolated EXTEM CT prolongation as a trigger for intervention in patients not on anticoagulant treatment. . Also, the presence of both EXTEM and FIBTEM CA5 derangements with a normal Li30 may justify administration of antifibrinolytic therapy, although this hypothesis needs to be validated prospectively. Furthermore, whether suppletion of factor V during trauma is beneficial is an important subject for future research.

In conclusion, ROTEM® derangements are a frequent observation at trauma presentation. An isolated EXTEM CT prolongation should not reflexively trigger therapy in patients not on anticoagulant therapy or not bleeding. In contrast, other ROTEM® derangements reflect a decrease in fibrinogen and factor V levels and a combination of EXTEM and FIBTEMCA5 derangements represents fibrinolysis, even when Li30 is normal. These results should be considered in current ROTEM based trauma algorithms.

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Figure legends

Figure 1. Coagulation factor levels stratified by ROTEM® derangement.

Median and interquartile ranges of (A) fibrinogen (B) factor II (C) factor V (D) factor VII (E) factor VIII (F) factor IX and (G) factor X and (H) factor XIII per coagulation group based on admission ROTEM® profile. An asterisk above the bar represents a statistically significant difference compared to the group of patients with a normal ROTEM® profile, * p<0.05, ** p<0.01, *** p<0.001.

Figure 2. Fibrinolysis marker levels stratified by ROTEM® derangement.

Median and interquartile ranges of (A) D-dimer (B) Alpha 2-antiplasmin (C) plasmin antiplasmin complexes and (D) Tissue plasminogen activator per coagulation group based on admission ROTEM® profile. An asterisk above the bar represents a statistically significant difference compared to the group of patients with a normal ROTEM® profile, * p<0.05, ** p<0.01, *** p<0.001.

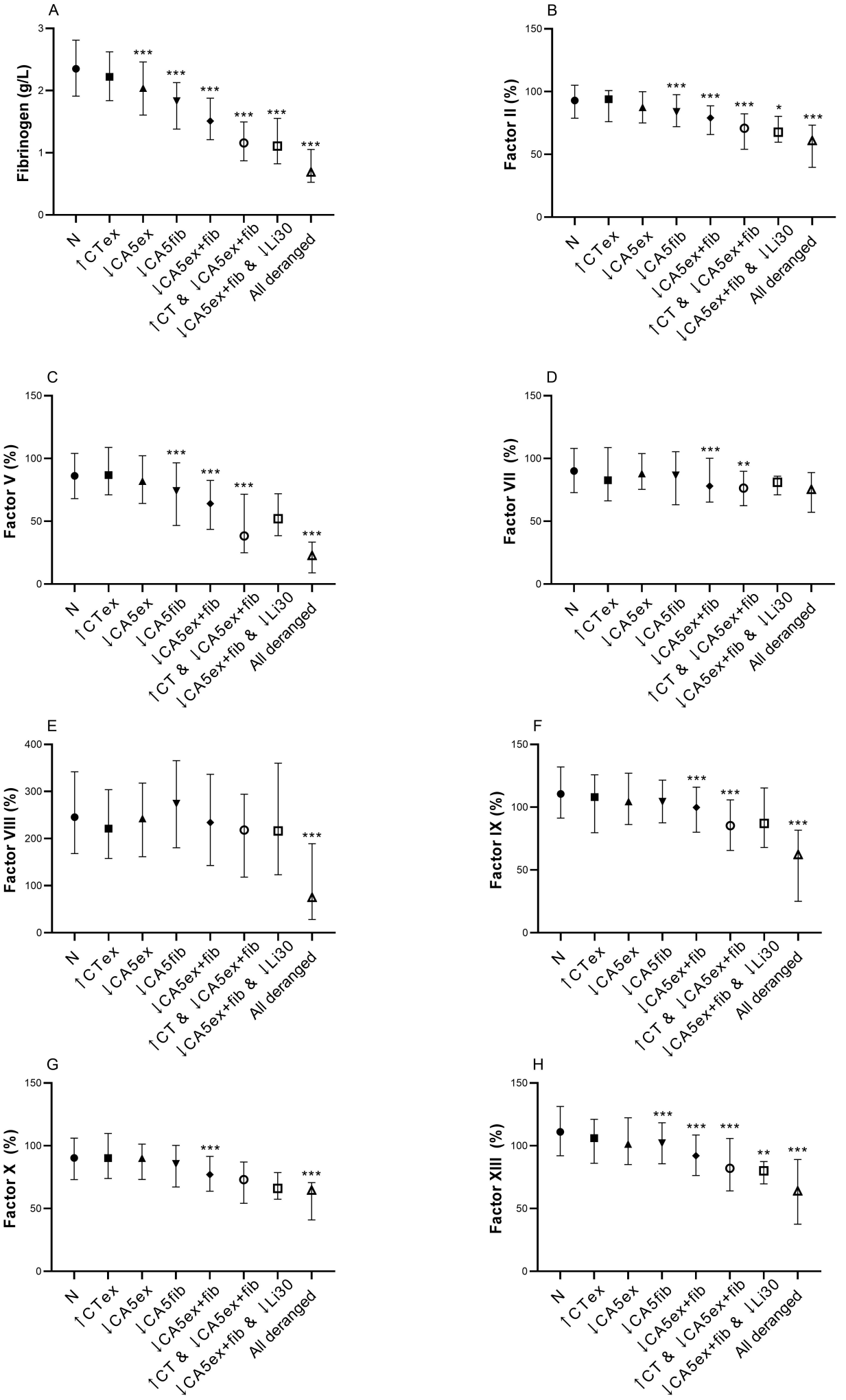
Legends to supplementary figures

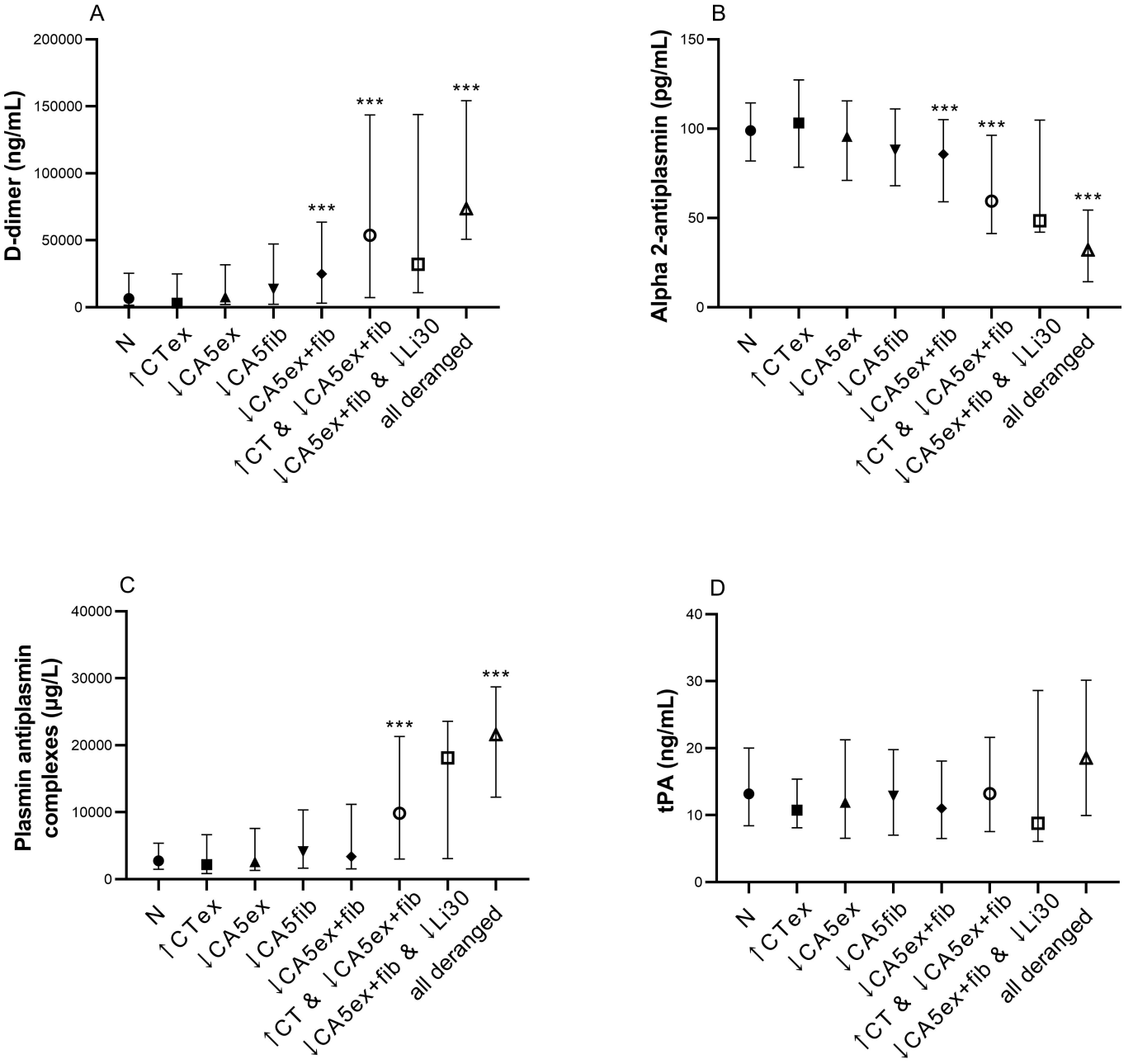
Figure A. Coagulation factor levels stratified by ROTEM® derangement with lysis at 30 minutes cut off (Li30) < 95%

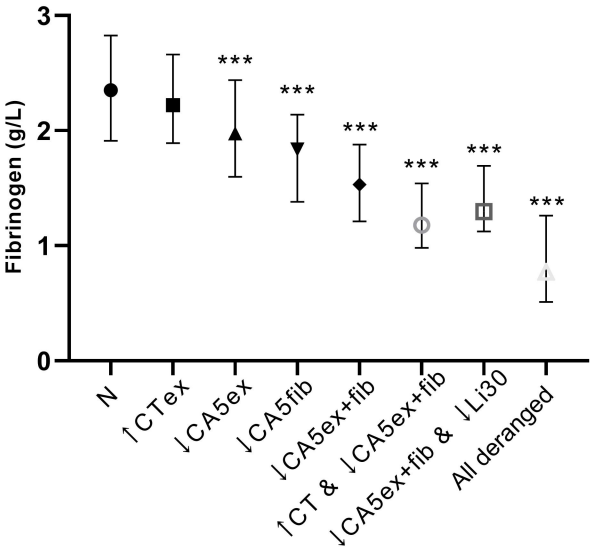
Median and interquartile ranges of fibrinogen, factor II, factor V, factor VII, factor IX and factor X per coagulation group based on admission ROTEM® profile. An asterisk above the bar represents a statistically significant difference compared to the group of patients with a normal ROTEM® profile, * p<0.05, ** p<0.01, *** p<0.001.

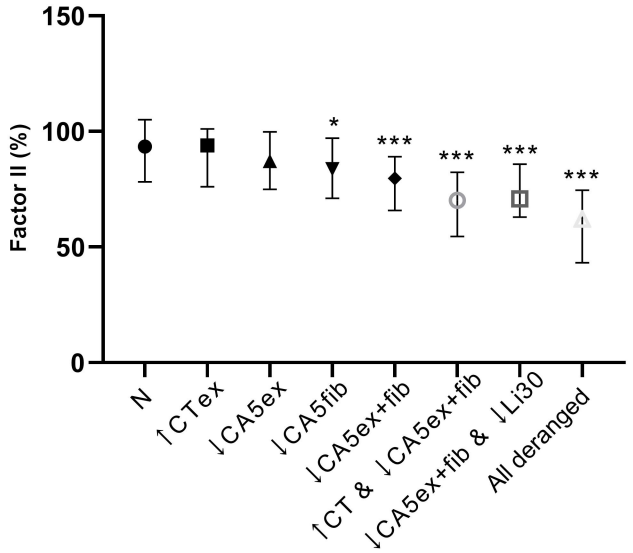
Figure B. Fibrinolysis marker levels stratified by ROTEM® derangement with lysis at 30 minutes cut off (Li30) < 95%

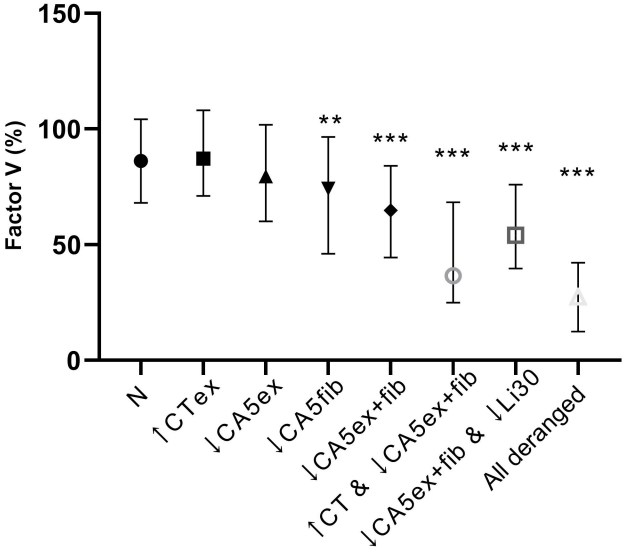
Median and interquartile ranges of D-dimer, Alpha 2-antiplasmin, Plasmin antiplasmin complexes and Tissue plasminogen activator per coagulation group based on admission ROTEM® profile. An asterisk above the bar represents a statistically significant difference compared to the group of patients with a normal ROTEM® profile, * p<0.05, ** p<0.01, *** p<0.001.

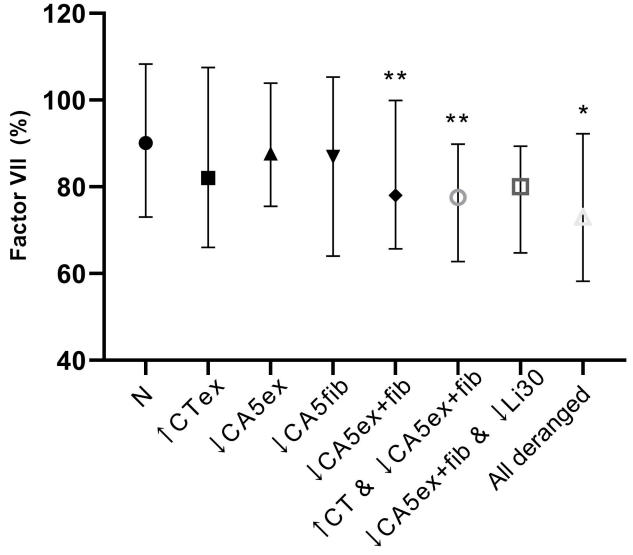

A
Fibrinogen (g/L)
B
Factor II (%)
C
Factor V (%)
D
Factor VII (%)
E
Factor VIII (%)
F
Factor IX (%)
G
Factor X (%)
H
Factor XIII (%)
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

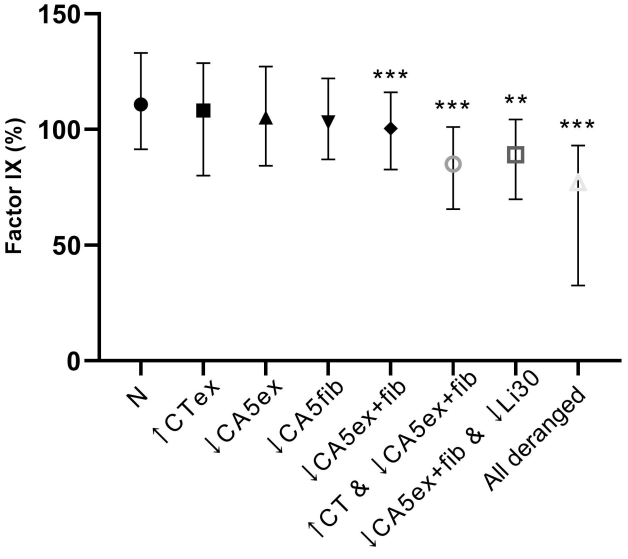

A
D-dimer (ng/mL)
200000
150000
100000
50000
0
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
all deranged
B
Alpha 2-antiplasmin (pg/mL)
150
100
50
0
***
***
***
C
Plasmin antiplasmin complexes (µg/L)
40000
30000
20000
10000
0
***
***
D
tPA (ng/mL)
40
30
20
10
0

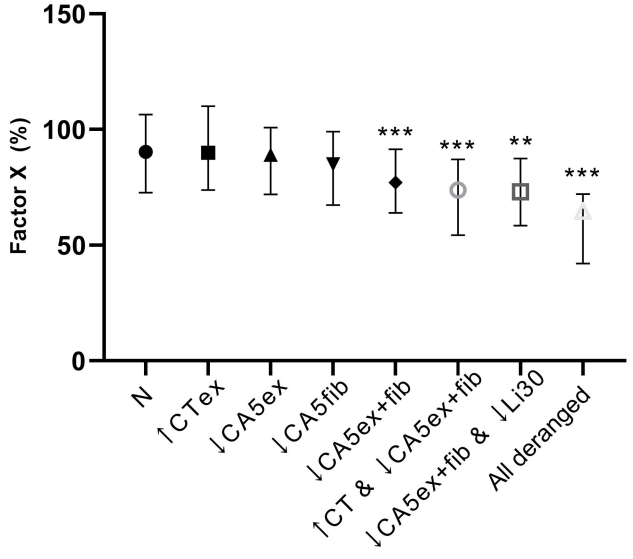

Fibrinogen (g/L)
3
2
1
0
***
***
***
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

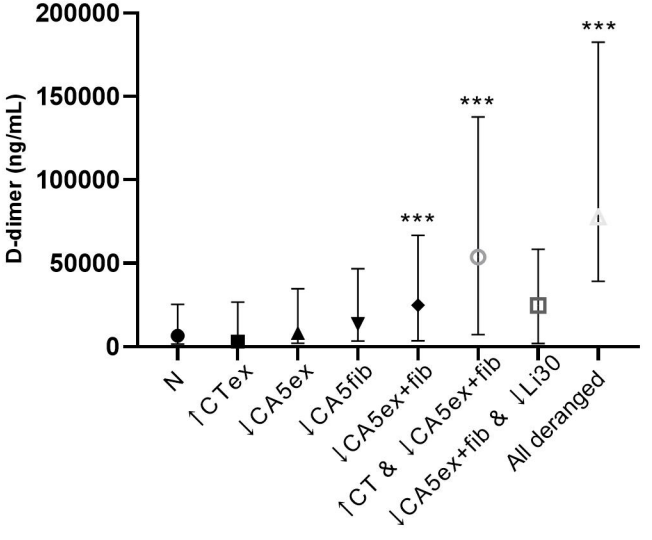

Factor II (%)
150
100
50
0
*
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

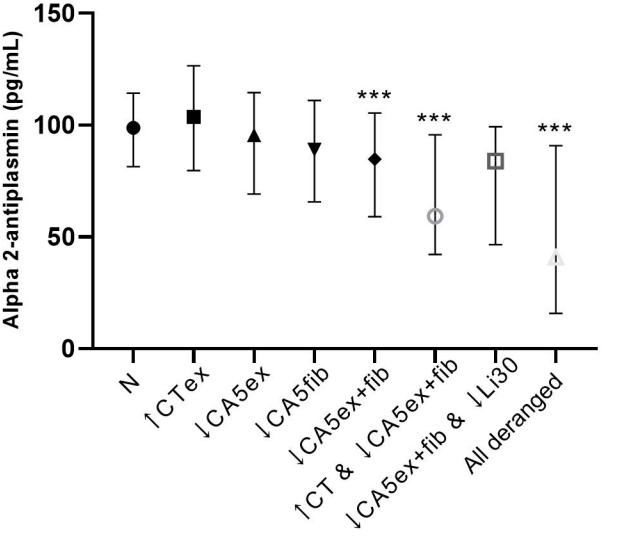

Factor V (%)
150
100
50
0
**
***
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

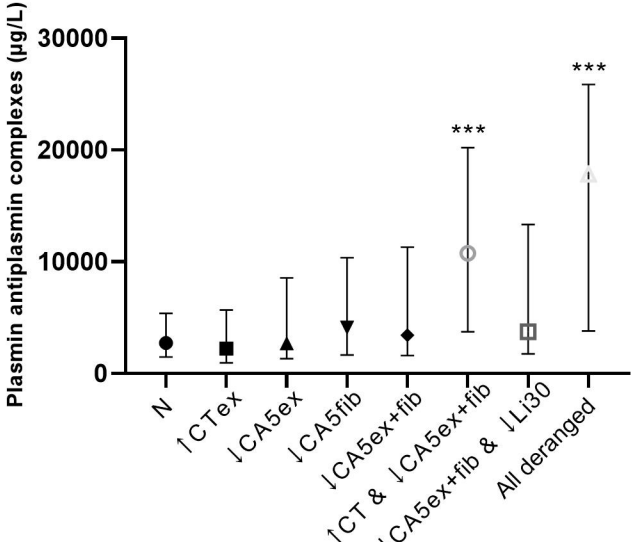

Factor VII (%)
120
100
80
60
40
**
**
*
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

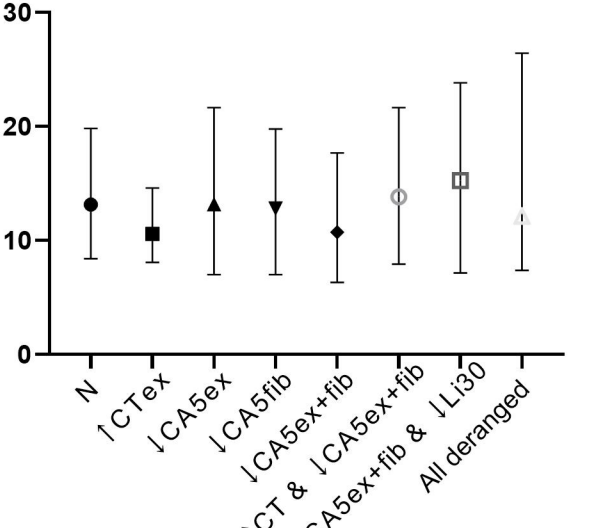

Factor IX (%)
150
100
50
0
***
***
**
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged


Factor X (%)
150
100
50
0
***
***
**
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged


D-dimer (ng/mL)
200000
150000
100000
50000
0
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged


Alpha 2-antiplasmin (pg/mL)
150
100
50
0
***
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged


Plasmin antiplasmin complexes (µg/L)
30000
20000
10000
0
***
***
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged


tPA (ng/mL)
30
20
10
0
N
↑CTex
↓CA5ex
↓CA5fib
↓CA5ex+fib
↑CT & ↓CA5ex+fib
↓CA5ex+fib & ↓Li30
All deranged

Supplemental tables

Supplemental Table 1. Difference of median and corresponding 95% CI (median difference bootstrapped confidence interval) for each of the ROTEM derangements groups compared to patients with a normal ROTEM profile.

	CTex>80s	**CA5ex<40mm & CA5fib≥10mm**	**CA5ex≥40mm & CA5fib<10mm**	**CA5ex<40mm & CA5fib<10mm**	**CTex>80s CA5ex<40mm & CA5fib<10mm**	**CTex≤80s CA5ex<40mm CA5fib<10mm & Li30<85%**	**CTex>80s CA5ex<40mm CA5fib<10mm & Li30<85%**
Fibrinogen (g/L)	-0.13 (-0.29 to 0.07)	-0.31 (-0.5 to -0.21)	-0.52 (-0.7 to -0.47)	-0.84 (-0.92 to -0.73)	-1.19 (-1.32 to -1.02)	-1.24 (-1.51 to -0.76)	-1.58 (-1.83 to -1.14)
Factor II (%)	1.10 (-6.80 to 3.50)	-5.30 (-9.50 to -1.30)	-9.00 (-11.30 to -3.80)	-13.90 (-18.10 to -12.00)	-22.10 (-28.00 to – 17.60)	-25.20 (-34.00 to – 10.90)	-31.90 (-44.20 to -26.40)
Factor V (%)	0.60 (-4.50 to – 11.50)	-4.20 (-10.30 to 1.90)	-12.0 (-19.2 to -7.70)	-22.2 (-27.40 to – 18.1)	-47.90 (-47.90 to -32.30)	-34.20 (-45.70 to -12.80)	-63.40 (-74.20 to -53.30)
Factor VII (%)	-7.40 (-10.10 to 6.00)	-2.10 (-6.70 to 4.50)	-3.50 (-10.40 to 0.10)	-12.10 (-14.20 to -5.70)	-13.70 (-21.10 to -7.80)	-9.10 (-23.20 to 4.80)	-14.70 (-29.10 to -5.80)
Factor VIII (%)	-22.9 (-54.90 to 5.00)	-1.10 (-34.70 to 15.60)	23.1 (-9.80 to 39.0)	-10.90 (-37.90 to 4.30)	-27.20 (-76.20 to – 15.80)	-27.90 (-91.70 to 61.90)	-169.00 (-196.00 to -96.20)
Factor IX (%)	-2.40 (-17.50 to 0.00)	-5.90 (-12.80 to 0.10)	-6.20 (13.20 to -2.40)	-10.90 (18.60 to -8.60)	-25.30 (-35.0 to -19.10)	-23.50 (-42.90 to -3.80)	-48.20 (-71.20 to -37.50)
Factor X (%)	-0.15 (-5.00 to 8.00)	-0.10 (-7.00 to 3.00)	-4.80 (-10.0 to -1.00)	-13.20 (-15.70 to -8.10)	-17.30 (-25.80 to -13.00)	-24.30 (-33.0 to -5.90)	-25.60 (-44.30 to -23.00)
Factor XIII (%)	-4.75 (-13.1 to 1.70)	-9.45 (-13.80 to -1.20)	-8.75 (-14.10 to -4.30)	-18.70 (-23.2 to -14.1)	-28.70 (-34.4 to -20.1)	-30.80 (-48.0 to -15.5)	-46.80 (-59.5 to -29.6)
D-dimer	-3621 (-3243 to 58.0)	1293 (-616 to 3088)	6887 (445 to 6126)	18312 (3615 to 15449)	47103 (14282 to 60774)	25351 (2875 to 76438)	72023 (48490 to 118896)
α2 antiplasmin	4.30 (-5.10 to 12.60)	-3.20 (-11.30 to 1.60)	-10.90 (-14.40 to -2.50)	-13.20 (-18.80 to -8.70)	-39.50 (-41.20 to -22.00)	-50.50 (-58.60 to -10.60)	-66.80 (-78.10 to -44.40)
PAP complexes	-564 (-998 to 69.20)	-129.00 (-479.0 to 412.0)	1349 (295 to 1593)	615 (110 to 1096)	7093 (2659 to 8660)	15379 (1213 to 18697)	18834 (11080 to 21054)
tPA	-2.42 (-4.00 to 0.204)	-1.27 (-2.84 to 0.953)	-0.325 (-2.23 to 0.889)	-2.14 (-3.13 to -0.454)	0.05 (-2.34 to 2.24)	-0.0762 (-5.89 to 16.7)	5.33 (-2.28 to 13.50)

Supplemental table 2. Baseline characteristics of ROTEM derangement groups with lysis defined as LI30 < 95%. Baseline characteristics and outcome of trauma patients admitted to the emergency department stratified by ROTEM derangement. Continuous data presented as median (25^{th} – 75^{th}) and categorical data as n(%). Statistical significance computed by a Kruskall Wallis for continuous data and chi square test for categorical data.

	Normal ROTEM®	**CTex>80s**	**CA5ex<40mm & CA5fib≥10mm**	**CA5ex≥40mm & CA5fib<10mm**	**CA5ex<40mm & CA5fib<10mm**	**CTex>80s CA5ex<40mm & CA5fib<10mm**	**CTex≤80s CA5ex<40mm CA5fib<10mm & Li30<95%**	**CTex>80s CA5ex<40mm CA5fib<10mm & Li30<95%**	**p value**
n	1042/1744 (59.7%)	81/1744 (4.6%)	118/1744 (6.8%)	169/1744 (9.7%)	193/1744 (11.1%)	72/1744 (4.1%)	35/1744 (2.0%)	34/1744 (1.9%)	
Age	43 (30 – 56)	42 (29 – 59)	43 (30 – 60)	35 (24 – 53)	34 (25 – 50)	32 (24 – 50)	35 (23 – 47)	35 (21 – 58)	<0.001
Male sex, %	749/1042 (71.9%)	65/81 (80.2%)	99/118 (83.9%)	148/169 (87.6%)	161/193 (83.4%)	61/72 (84.7%)	29/35 (82.9%)	26/34 (76.5%)	<0.001
Blunt injury, %	792/913 (86.7%)	36/49 (73.5%)	80/99 (80.8%)	126/150 (84.0%)	153/177 (86.4%)	54/61 (88.5%)	27/31 (87.1%)	27/30 (90.0%)	0.183
TBI, %	218/975 (22.4%)	18/80 (22.5%)	32/109 (29.4%)	56/159 (35.2%)	64/188 (34.0%)	31/72 (43.1%)	10/31 (32.3%)	15/32 (46.9%)	<0.001
Injury severity score	10 (5 – 21)	10 (4 – 22)	13 (5 – 25)	17 (9 – 26)	20 (9 – 30)	28 (15 – 41)	33 (7 - 38)	32 (15 – 43)	<0.001
Lactate	1.9 (1.3 – 2.8)	2.0 (1.5 – 2.9)	2.0 (1.2 – 3.3)	2.4 (1.4 – 3.7)	2.2 (1.4 – 3.5)	3.5 (1.8 – 5.9)	3.6 (1.5 – 8.2)	4 (1.8 – 9.7)	<0.001
Outcome									
≥4 Red blood cells	91/1028 (8.9%)	7/81 (8.6%)	19/117 (16.2%)	36/167 (21.6%)	53/192 (27.6%)	30/72 (41.7%)	18/35 (51.4%)	15/33 (45.5%)	<0.001
12 hour mortality, %	4/1042 (0.4%)	0/80 (0%)	3/118 (2.5%)	4/169 (2.4%)	6/193 (3.1%)	5/72 (6.9%)	4/35 (11.4%)	12/34 (35.3%)	<0.001
28 day mortality, %	42/1032 (4.1%)	2/80 (2.5%)	12/116 (10.3%)	19/166 (11.4%)	26/193 (13.5%)	25/72 (34.7%)	6/35 (17.1%)	21/33 (63.6%)	<0.001

Supplemental Table 3. Binary logistic regression model with 12 hour mortality as outcome variable and age, sex, lactate, injury severity score and ROTEM derangement group as predictor variables. Since ROTEM derangement group is a categorical variable, dummy variables were created for the binary logistic regression with patients with a normal ROTEM profile as a reference group. The reference for sex is male.

Variables in the equation			
	B	p-value	OR (95% CI)
Constant	-8.612	<0.001	
Age	0.023	0.027	1.023 (1.002 – 1.043)
Sex	0.37	0.45	1.451 (0.56 – 3.80)
Lactate	0.102	0.009	1.12 (1.025 – 1.20)
Injury severity score	0.068	<0.001	1.07 (1.043 – 1.10)
ROTEM derangement group		0.009	
1. ↑CT EXTEM	-15.610	1.0	-
2. ↓CA5 EXTEM	1.91	0.009	6.76 (1.61 – 28.49)
3. ↓CA5 FIBTEM	1.58	0.030	4.86 (1.17 – 20.20)
4. ↓CA5 EXTEM & FIBTEM	1.42	0.035	4.13 (1.11 – 15.43)
5. ↑CT & ↓CA5 EXTEM & FIBTEM	1.99	0.005	7.32 (1.85 – 28.91)
6. ↓CA5 EXTEM & FIBTEM & ↓ lysis at 30 minutes	3.35	0.001	28.42 (3.70 – 218.29)
7. All deranged	3.00	<0.001	19.29 (3.91 – 95.04)