1   **DATA-DRIVEN DEVELOPMENT OF ROTEM AND TEG ALGORITHMS FOR THE**

2   **MANAGEMENT OF TRAUMA HEMORRHAGE - A PROSPECTIVE**

3   **OBSERVATIONAL MULTICENTER STUDY**

4

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SHORT RUNNING HEAD: VHA algorithms for trauma hemorrhage.

1   **ABSTRACT:**

2   *Objective:* Developing pragmatic data-driven algorithms for management of trauma induced

3   coagulopathy (TIC) during trauma hemorrhage for viscoelastic hemostatic assays (VHAs).

4   *Summary Background Data:* Admission data from conventional coagulation tests (CCT),

5   rotational thrombelastometry (ROTEM) and thrombelastography (TEG) were collected

6   prospectively at 6 European trauma centers during 2008-2013.

7   *Methods:* To identify significant VHA parameters capable of detecting TIC (defined as INR >

8   1.2), hypofibrinogenemia ($< 2.0g/L$) and thrombocytopenia (< 100 $x10^9/L$), univariate

9   regression models were constructed. Area under the curve (AUC) was calculated, and

10   threshold values for TEG and ROTEM parameters with 70% sensitivity were included in the

11   algorithms.

12   *Results:* 2287 adult trauma patients (ROTEM: 2019 and TEG: 968) were enrolled. FIBTEM

13   clot amplitude at 5 minutes (CA5) had the largest AUC and 10mm detected

14   hypofibrinogenemia with 70% sensitivity. The corresponding value for Functional Fibrinogen

15   (FF) TEG Maximum Amplitude (MA) was 19mm. Thrombocytopenia was similarly detected

16   using the calculated threshold EXTEM-FIBTEM CA5 30mm. The corresponding rTEG-FF

17   TEG MA was 46mm. TIC was identified by EXTEM CA5 41mm, rTEG MA 64mm (80%

18   sensitivity). For hyperfibrinolysis, we examined the relationship between viscoelastic lysis

19   parameters and clinical outcomes, with resulting threshold values of 85% for EXTEM Li30

20   and 10% for rTEG Ly30.

21   Based on these analyses we constructed algorithms for ROTEM, TEG and CCTs to be used in

22   addition to ratio driven transfusion and tranexamic acid.

23   *Conclusion:* We describe a systematic approach to define threshold parameters for ROTEM

24   and TEG. These parameters were incorporated into algorithms to support data-driven

1   adjustments of resuscitation with therapeutics, to optimize damage control resuscitation

2   practice in trauma.

3

4   **MINI-ABSTRACT:**

5   This large cohort study defines threshold parameters for the treatment of trauma-induced

6   coagulopathy with ROTEM and TEG in trauma. We derived new precision algorithms for the

7   use of ROTEM and TEG to individualize care and optimize standard empiric hemostatic

8   resuscitation practice.

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1 **INTRODUCTION**

2 Trauma remains one of the world's leading causes of death [1] with upwards of 2 million

3 people dying from trauma hemorrhage each year [1,2]. Advances in our understanding of

4 trauma-induced coagulopathy (TIC) and new approaches to resuscitation have led to large

5 improvements in outcomes [3]. However even in the best centers, one in four trauma patients

6 with severe bleeding die, and overall mortality may approach 50% [4]. Current resuscitation

7 often manages coagulopathy empirically, is non-specific and does not correct a pre-existing

8 coagulopathy [5,6]. A targeted, precision medicine approach to the treatment of TIC may lead

9 to improved outcomes while reducing overall requirements for red cells and component

10 therapies.

11

12 TIC has multiple phenotypes and individual patients may present with different forms of

13 coagulopathy at different times in their clinical course [7,8]. Contemporary resuscitation of

14 bleeding trauma patients delivers volume resuscitation through an empiric, balanced

15 transfusion of red blood cells, plasma and platelets in proportions approximating that of

16 whole blood [9]. While this approach reduces the development of dilutional coagulopathy, it

17 does not treat any underlying coagulopathy and does not fully support hemostasis in patients

18 who require large volumes of transfusion [5,6]. The targeted correction of underlying

19 coagulopathy using conventional coagulation tests (CCTs) is attractive in principle and

20 supported by small trials [10,11]. However, the logistics of providing laboratory results in a

21 suitable timeframe are challenging [11,12]. This has led to the suggestion of a hybrid

22 approach, starting with empiric therapy and switching to an individualized, precision

23 approach as soon as coagulation assessments are available [13-15]. This approach ideally

24 requires rapidly available point of care assessments of coagulopathy and has resulted in

25 renewed interest in viscoelastic hemostatic assays (VHAs) to diagnose the underlying

1   hemostatic deficiencies and to guide coagulation support. However, there is currently

2   insufficient data to support the use of VHAs in trauma hemorrhage [16-20]. While a number

3   of small studies shows VHA results can predict transfusion requirements or guide therapy,

4   there is minimal evidence for parameters to guide the administration of coagulation

5   therapeutics during active trauma hemorrhage [21-23].

6

7   The overall objective of this study was to develop pragmatic data-driven algorithms for the

8   VHAs in the management of TIC during trauma hemorrhage. Our first aim was to determine,

9   for both thromboelastometry (ROTEM®) and thromboelastography (TEG®), parameters and

10   thresholds with high detection rate for TIC. We then aimed to determine the optimum

11   parameters to guide therapy – specifically thresholds to guide the treatment of

12   hypofibrinogenemia, thrombocytopenia, coagulation factor deficiency and hyperfibrinolysis.

13   Finally, we wished to synthesize these findings into pragmatic algorithms for clinical practice.

14

15   **METHODS**

16   *Study design*

17   This study was part of the TACTIC (Targeted Action for Curing Trauma Induced

18   Coagulopathy) program [24] of the International Trauma Research Network (INTRN) [25].

19   The prospective multinational observational study ACIT (Activation of Coagulation and

20   Inflammation in Trauma) was the research platform for the study. Patients were recruited

21   prospectively at six major trauma centers in five different countries - the UK, Denmark,

22   Germany, the Netherlands and Norway.

23   *Participants*

24   Adult trauma patients who met the local criteria for full trauma team activation were eligible

25   for inclusion. Patients who received more than 2000 mL of fluids before arrival in the

1   emergency department (ED) or who arrived more than 2 hours from time of injury were

2   excluded, as were patients who were pregnant, had known liver failure, pre-existing bleeding

3   disorders or were taking oral anticoagulants other than aspirin. Patients who had received

4   blood products or Tranexamic Acid (TXA) before admission were not excluded. Initial

5   consent was provided by a physician independent of the study. Written informed consent was

6   obtained as soon as possible from the patients or their next of kin. The study was approved by

7   local ethical authorities and performed in accordance with local ethical regulations and the

8   Declaration of Helsinki.

9   *Data collection*

10   Patient demographics, time and mechanism of injury, pre-hospital fluid administration, vital

11   signs on admission, total amount of fluids and blood products administered within the first 12

12   hours, and CCTs on admission were collected prospectively. Injury severity was scored when

13   relevant information was available. TEG and ROTEM values were recorded electronically

14   and later transferred manually to the case report form (CRF).

15   *Sampling techniques and measurements*

16   ACIT first began recruiting patients in 2008 with ROTEM, and TEG analyses were added in

17   parallel from 2013. Blood samples were collected within 20 minutes of arrival in the ED.

18   Samples for TEG, ROTEM and CCTs were collected in citrated tubes. Samples for blood gas

19   analyses were collected in heparinized syringes in accordance with local routines. TEG and

20   ROTEM were performed within one hour, at 37°C by dedicated study personnel using the

21   TEG 5000® Thrombelastograph Hemostasis Analyzer (Haemonetics Corp., Braintree, MA,

22   US) and the ROTEM Delta® (TEM international GmbH, Munich, Germany). The

23   methodology and the parameters of TEG and ROTEM have been described previously

24   [26,27].

1 *ROTEM, TEG and CCT analyses*

2 The ROTEM assays used in this study were the EXTEM and FIBTEM, both activated by

3 tissue factor derived from rabbit brain, with cytochalasin D added to the FIBTEM sample for

4 platelet inhibition [27]. TEG assays were standard TEG, where the sample is activated by

5 Kaolin, Rapid TEG (rTEG) where the sample is activated by both Kaolin and tissue factor,

6 and Functional Fibrinogen TEG (FF TEG) where lyophilized tissue factor with a platelet

7 inhibitor Abciximab (a glycoprotein IIb/IIIa-inhibitor) is added for platelet inhibition to

8 isolate the fibrin component of the clot [27]. The CCTs were Prothrombin Time (PT),

9 fibrinogen concentration and platelet count (PLT). PT was converted to international

10 normalized ratio (INR) in accordance with the specific reagents and device characteristics in

11 the respective laboratories. Fibrinogen was measured by the Clauss method [28].

12 *Definitions*

13 We defined the presence of TIC as INR > 1.2 [12]; hypofibrinogenemia was defined as

14 fibrinogen concentration < 2.0 g/L [9]; and thrombocytopenia as a platelet count below 100 x

15 10^9 /L [9,19]. In the absence of an accepted laboratory definition of hyperfibrinolysis in

16 trauma patients we aimed to determine threshold values for treatment through their

17 relationship with mortality and transfusion requirements.

18 *Statistical analyses*

19 Multiple imputations were performed on all TEG and ROTEM data, to deal with the missing

20 data. Predictive mean matching was performed and 10 imputation sets were constructed. The

21 imputations were tested using graphical density plots where the imputed data was plotted

22 separately from the original data and convergence was checked. The outcomes from the

23 analyses were pooled using Rubin's rule [29]. Statistical analyses were also performed with

24 non-imputed data, to confirm that multiple imputations had not introduced unacceptable bias.

25

1 To identify significant VHA parameters capable of identifying TIC, hypofibrinogenemia and

2 thrombocytopenia univariate regression models were constructed for these outcomes and

3 areas under the curves (AUCs) were calculated. The platelet component was examined by

4 subtracting the FIBTEM clot amplitude at 5 minutes (CA5) from the EXTEM CA5 and the

5 FF TEG maximum amplitude (MA) from the rTEG MA. Threshold values for TEG and

6 ROTEM parameters with sensitivities approaching 60%, 70%, 80% and 90% were calculated

7 with corresponding specificities, Negative Predictive Values (NPVs) and Positive Predictive

8 Values (PPVs).

9

10 The multiple imputations and the univariate analyses were performed with R version 3.1.2.

11 All other analyses were performed with SPSS version 23 (IBM Corporation, United States).

12

13 *Algorithm development*

14 All centers in the TACTIC program have empiric replacement therapy of high-dose plasma

15 and platelet transfusions given alongside red blood cell transfusions as the basis of their major

16 hemorrhage protocol [3,19,30]. All centers also empirically give tranexamic acid to all

17 patients activating the major hemorrhage protocol [31,32]. This concept of personalized

18 hemostasis control augmenting baseline empiric therapy has been previously described as the

19 'Copenhagen Concept' [13-15].

20

21 Algorithms were based on the principles that they should be able to guide hemostatic therapy,

22 namely fibrinogen replacement, platelet transfusions, plasma procoagulant supplementation

23 and antifibrinolytic therapy. Algorithms were also to be as pragmatic and easy to follow as

24 possible, using parameters that were not only strongly associated with underlying

25 coagulopathy states, but also had face validity to clinicians. The key outputs of this study are

26 the trigger thresholds for administration of coagulation therapies. We selected the earliest

1   available parameter that provided the required information and threshold levels that were at

2   least 70% sensitive despite potentially low specificity, as the interventions are known to carry

3   generally acceptable risk in a life-threatening setting. Threshold values were also selected to

4   be easier to recall if small changes (e.g. rounding up or down) would not significantly alter

5   the performance of individual parameters. For the therapies and doses associated with these

6   thresholds we chose best practice levels from current guidelines and evidence.

7

8   **RESULTS**

9   From August 2008 to December 2014, a total of 2287 patients were recruited to ACIT across

10   6 sites. ROTEM was performed in 2019 patients, while 968 patients had TEG assessments on

11   admission. Patient demographics, injury characteristics, admission parameters and outcomes

12   were similar in both cohorts (Table 1). Overall approximately 6.5% of the cohort was

13   coagulopathic by INR on admission and 15% required at least 4 units of red cell transfusions

14   in the first 12 hours.

15

16   *Detection of Hypofibrinogenemia*

17   For ROTEM, the FIBTEM CA5 reported the highest AUC for hypofibrinogenemia (0.80)

18   (Figure 1) (see Table, Supplemental Digital Content 1: Detection of Hypofibrinogenemia;

19   AUCs and 95% CI). As expected, FIBTEM maximum clot firmness (MCF) also performed

20   well with an AUC of 0.78 (Figure 1) (see Table, Supplemental Digital Content 1: Detection of

21   Hypofibrinogenemia; AUCs and 95% CI). A FIBTEM CA5 threshold of 10mm had a

22   sensitivity of 70%, specificity of 76% and NPV of 88% for the detection of

23   hypofibrinogenemia (Table 2).

24   For TEG the rTEG MA was the best performing variable with an AUC of 0.76 (Figure 1) (see

25   Table, Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95%

26   CI). Both FF TEG MA and Kaolin-TEG MA had AUCs of 0.72 (Figure 1) (see Table,

1   Supplemental Digital Content 1: Detection of Hypofibrinogenemia; AUCs and 95% CI). An

2   FF-TEG MA of 19 mm had a sensitivity of 70% and specificity of 59% for the detection of

3   hypofibrinogenemia, with an NPV of 89% (Table 2).

4

5   *Detection of Thrombocytopenia*

6   Only 44 (2%) ROTEM patients and 17 (1,5%) TEG patients presented with low platelet

7   counts. The EXTEM-FIBTEM CA5 had an AUC of 0.75 for identifying patients with low

8   platelet counts and EXTEM-FIBTEM MCF performed similarly with an AUC of 0.70 (see

9   Table, Supplemental Digital Content 2: Detection of low platelets; AUCs and 95% CI) (see

10   Figure, Supplemental Digital Content 3: Receiver Operator Characteristic (ROC) curves,

11   ROTEM and TEG, thrombocytopenia). An EXTEM-FIBTEM CA5 threshold of 30 mm had

12   a sensitivity of 74% with a specificity of 63% and a NPV of 99% (Table 3).

13   For TEG the subtracting amplitude of FF TEG MA from the rTEG MA had an AUC of 0.54

14   (See Table, Supplemental Digital Content 2: Detection of low platelets; AUCs and 95% CI)

15   (See Figure, Supplemental Digital Content 3: Receiver Operator Characteristic (ROC) curves,

16   ROTEM and TEG, thrombocytopenia). A rTEG – FF TEG MA threshold of 45 mm had a

17   sensitivity of 65% with a specificity of 32% and NPV of 98% (Table 3).

18

19   *Detection of Hyperfibrinolysis*

20   To identify thresholds for the detection of hyperfibrinolysis we examined the relationship

21   between viscoelastic lysis parameters and clinical outcomes. For ROTEM maximum lysis

22   (ML) there was a step-change in mortality in patients with a ML above 20% (ML %: $\leq 20\%$

23   vs > 20% - 9.5% vs 50.0%, $p < 0.001$). At 30 minutes, the ROTEM Lysis Index (LI30)

24   parameter showed a similar mortality outcome threshold at 85% (LI30: < 85% vs $\geq 85\%$ -

25   76.2% vs 10.8%, $p < 0.001$). Only 3.5% of those with an LI30 above 85 % subsequently

1   developed an ML > 20%, of which 4 patients died (10.5% mortality - not significantly

2   different from LI30 ≥ 85% or ML < 20% groups). Mean 24-hour packed red blood cell

3   (PRBC) requirements also increased markedly at LI30 levels below 85% (LI30: < 85% vs ≥

4   85% - 14 vs 7 units, p < 0.001).

5   For TEG detection of hyperfibrinolysis, there was an increase in mortality at rTEG clot lysis

6   at 30 minutes (LY30) values above 10% (LY30: ≤ 10% vs > 10% - 8.8% vs 60.0%, p <

7   0.001). There was an associated increase in PRBC requirements at this threshold: (LY30: ≤

8   10% vs >10% - 2 vs 10 units, p < 0.001).

9

10   *Detection of Coagulopathy*

11   For ROTEM, EXTEM CA5 had the greatest AUC (0.78) for identification of INR >1.2 which

12   was closely followed by the MCF, clot formation time (CFT), α-angle and clotting time (CT)

13   (0.76, 0.76, 0.75 and 0.72, respectively) (Figure 2) (See Table, Supplemental Digital Content

14   4: Detection of Coagulopathy; AUCs and 95% CI). A CA5 threshold of 41 mm had a

15   sensitivity of 73% for the detection of coagulopathy with a specificity of 70%, and a NPV of

16   97% (Table 4).

17

18   For detection of coagulopathy with TEG the highest AUC was with the FF TEG reaction time

19   (r), α-angle and MA parameters, all with an AUC of 0.73 (Figure 2) (See Table, Supplemental

20   Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). The rTEG r performed

21   similarly with an AUC of 0.71, with rTEG activated clotting time (ACT) and MA at 0.69 and

22   0.67 respectively (Figure 2) (See Table, Supplemental Digital Content 4: Detection of

23   Coagulopathy; AUCs and 95% CI). The best performing Kaolin-TEG variable was the MA

24   with an AUC of 0.71. The Kaolin-TEG r had a much lower AUC at 0.58 (See Table,

25   Supplemental Digital Content 4: Detection of Coagulopathy; AUCs and 95% CI). An rTEG

1   ACT of 121 had a sensitivity of 63 % for detection of coagulopathy with a specificity of 68%

2   and a NPV of 96% (Table 4).

3

4   *Algorithm Development*

5   Based on the analyses above we constructed management algorithms for ROTEM, TEG and

6   CCTs (Fig 3a, b and c respectively) to be used in addition to baseline damage control

7   resuscitation (empiric high-dose plasma and platelets and baseline administration of

8   tranexamic acid).

9

10   ROTEM

11   Given the principles of timely availability, adequate performance and pragmatic triggers, we

12   defined a FIBTEM CA5 threshold of 10 mm for the dosing of additional fibrinogen (Table 2).

13   For administering additional platelets transfusions, we used the EXTEM CA5 – FIBTEM

14   CA5 threshold of < 30 mm. To identify those patients who may require additional plasma

15   despite sufficient replacement of fibrinogen and platelets we selected a standard EXTEM CT

16   value of > 80 seconds in the presence of a non-coagulopathic EXTEM CA5 (> 40 mm).

17   Additional TXA would be administered when EXTEM LI30 < 85%.

18

19   TEG

20   We constructed a TEG algorithm using the same principles. We selected a FF TEG < 20 mm

21   as a threshold value for additional fibrinogen (Table 2). For other parameters, rTEG

22   parameters were used rather than Kaolin TEG for their timeliness [33], given there was no

23   significant loss of sensitivity or specificity across these tests. We chose a rTEG – FF TEG

24   MA below 45mm as a threshold for giving additional platelet transfusions (Table 3). For

25   additional plasma, we again used a standard rTEG ACT > 120 seconds' threshold provided

1   there was no indication for fibrinogen or platelets (i.e. rapid TEG MA > 65 mm (Table 4)). A

2   Rapid TEG LY30 > 10% was used as a threshold value for additional TXA.

3

4   For both ROTEM and TEG algorithms the suggested therapeutic interventions are the same

5   and based on current best practice guidance or evidence. For fibrinogen supplementation, we

6   suggest a replacement dose of 4g (usually as cryoprecipitate or fibrinogen concentrate) [34];

7   for low platelet levels, we suggest 1 pool of platelet transfusions; for evidence of low

8   procoagulant activity we suggest additional plasma as an extra 4 units of FFP [6]; and for

9   evidence of hyperfibrinolysis we suggest an additional 1g bolus of tranexamic acid [35,36].

10

11   **DISCUSSION**

12   We have defined accurate, rapidly available parameters that identify the key coagulation

13   derangements that are corrected by available therapeutics, together with threshold values for

14   their administration. With this large prospective cohort study across five countries we have

15   developed data-driven algorithms for individualized hemostasis management of trauma

16   patients. We adopted a pragmatic approach focusing on available hemostatic therapies as an

17   addition to a baseline damage control resuscitation. The empiric ratio MTP continues until

18   hemostasis, adding the available hemostatic therapies as guided by TEG/ROTEM or CCT as

19   soon as the test results are available. In studying ROTEM and TEG devices in parallel we

20   have produced algorithms applicable to all centers regardless of which device is available.

21   This study therefore fills a considerable evidence gap in the role of viscoelastic hemostatic

22   assays in the management of bleeding trauma patients [16-18,20,21].

23

24   The parameters proposed in this study will need further validation in subsequent studies. For

25   internal validation, the ACIT study continues to run across the INTRN sites. External

1   validation will be needed from other centers and networks, especially those in other countries

2   and healthcare systems. Although the parameters and thresholds used in our algorithms were

3   data driven, there was limited evidence for the choice or dose of therapeutic agents. We used

4   a combination of available evidence, guidelines and intrinsic expertise alongside the desire for

5   the algorithms to be broadly applicable at an international level. Each individual agent and

6   dose is worthy of further study. As a whole, the algorithms are being taken forward by the

7   TACTIC partners into a randomized controlled trial (RCT) of viscoelastic assays versus

8   conventional coagulation therapy (the iTACTIC trial, ClinicalTrials.gov Identifier:

9   NCT02593877). This should provide evidence for the whole algorithm approach, which can

10   be refined and updated with future investigations.

11

12   There are several limitations to our study in addition to the lack of a separate validation set.

13   Despite the large cohorts and high injury severity scores, the number of coagulopathic and

14   massively bleeding patients was around 15%. Some specific derangements, such as low

15   platelet counts, were very rare, especially as we focused on the first sample drawn after

16   admission. This will lead to bias to the negative predictive value of a parameter and

17   potentially under-represent their positive predictive value and overall accuracy. Thresholds

18   for hyperfibrinolysis had to be determined from clinical correlates in the absence of a

19   definitive laboratory comparator test. The prehospital use of tranexamic acid will have

20   contributed to the relatively low observed rates of admission hyperfibrinolysis, but should not

21   have affected the actual threshold levels we calculated. Further external validation studies

22   should be performed to confirm the applicability of these criteria for antifibrinolytic

23   administration.

24   Some of the differences in performance between ROTEM and TEG parameters are also likely

25   to be due to the difference in sample sizes between the two cohorts. As we aimed to develop

1   internationally relevant algorithms, we did not explore between-center variations in

2   prehospital or in-hospital practices. However, overall the clinical and transfusion practices at

3   the centers are more similar than they are different, and all adhere to modern practices of

4   damage control resuscitation [30]. We therefore believe the study findings represent the real-

5   world situation and are thus broadly applicable across similar healthcare systems.

6

7   **CONCLUSION**

8   In this large prospective cohort study, we have determined the clinically optimal tests,

9   parameters and thresholds to guide hemostatic therapies in trauma patients. We present

10   algorithms for a precision approach to TIC, augmenting standard damage control resuscitation

11   practice. These algorithms are being taken forward for evaluation in the iTACTIC

12   multicenter randomized controlled trial of viscoelastic assays versus CCTs on clinical

13   outcomes in trauma hemorrhage.

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1   **TABLES:**

2   Table 1: Baseline demographics, injury characteristics, admission parameters, transfusion

3   requirement and outcomes

4   Table 2: Detection of Hypofibrinogenemia (Fibrinogen < 2.0 g/L)

5   Table 3: Detection of Thrombocytopenia (platelet count < 100 x 10^9/L)

6   Table 4: Table 4: Detection of Coagulopathy (INR > 1.2)

7

8   **FIGURES:**

9   Figure 1: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG,

10   hypofibrinogenemia (fibrinogen < 2,0 g/L).

11   Figure 2: Receiver Operator Characteristic (ROC) curves, ROTEM and TEG, Coagulopathy

12   (INR > 1,2)

13   Figure 3: Algorithms

14

15   **SUPPLEMENTAL DIGITAL CONTENT**

16   Supplemental Digital Content 1: Table: Detection of Hypofibrinogenemia

17   (fibrinogen < 2.0 g/L); AUCs and 95% CI

18   Supplemental Digital Content 2: Table: Detection of low platelets (platelets < 100 x 10^9/L);

19   AUCs and 95% CI

20   Supplemental Digital Content 3: Figure: Receiver Operator Characteristic (ROC) Curves,

21   ROTEM and TEG, Thrombocytopenia

22   Supplemental Digital Content 4: Table: Detection of Coagulopathy (INR > 1.2); AUCs and

23   95% CI

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