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Authors

Keyloun, John

Le, Tuan

Moffatt, Lauren

et al.

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Comparison of Rapid-, Kaolin-, and Native-TEG Parameters in Burn Patient Cohorts With Acute Burn-induced Coagulopathy and Abnormal Fibrinolytic Function

John W. Keyloun, MD[1,2]; Tuan D. Le, MD, DPH[3,4]; Lauren T. Moffatt, PhD[2,5]; Thomas Orfeo, PhD[6]; Melissa M. McLawhorn, RN, BSN[2]; Maria-Cristina Bravo, PhD[6]; Shawn Tejiram, MD[1]; the SYSCOT Study Group[†]; Jeffrey W. Shupp, MD[1,2,7]; Anthony E. Pusateri, PhD[*,8,9]

Although use of thromboelastography (TEG) to diagnose coagulopathy and guide clinical decision-making is increasing, relative performance of different TEG methods has not been well-defined. Rapid-TEG (rTEG), kaolin-TEG (kTEG), and native-TEG (nTEG) were performed on blood samples from burn patients presenting to a regional center from admission to 21 days. Patients were categorized by burn severity, mortality, and fibrinolytic phenotypes (Shutdown [SD], Physiologic [PHYS], and Hyperfibrinolytic [HF]). Manufacturer ranges and published TEG cutoffs were examined. Concordance correlations (Rc) of TEG parameters (R, α-angle, maximum amplitude [MA], LY30) measured agreement and Cohen's Kappa (κ) determined interclass reliability. Patients (n = 121) were mostly male (n = 84; 69.4%), with median age 40 years, median TBSA burn 13%, and mortality 17% (n = 21). Severe burns (≥40% TBSA) were associated with lower admission α-angle for rTEG (P = .03) and lower MA for rTEG (P = .02) and kTEG (P = .01). MA was lower in patients who died (nTEG, P = .04; kTEG, P = .02; rTEG, P = .003). Admission HF was associated with increased mortality (OR, 10.45; 95% CI, 2.54–43.31, P = .001) on rTEG only. Delayed SD was associated with mortality using rTEG and nTEG (OR 9.46; 95% CI, 1.96–45.73; P = .005 and OR, 6.91; 95% CI, 1.35–35.48; P = .02). Admission TEGs showed poor agreement on R-time (Rc, 0.00–0.56) and α-angle (0.40 to 0.55), and moderate agreement on MA (0.67–0.81) and LY30 (0.72–0.93). Interclass reliability was lowest for R-time (κ, −0.07 to 0.01) and α-angle (−0.06 to 0.17) and highest for MA (0.22-0.51) and LY30 (0.29-0.49). Choice of TEG method may impact clinical decision-making. rTEG appeared most sensitive in parameter-specific associations with injury severity, abnormal fibrinolysis, and mortality.

Key words: burns; thromboelastography; TEG; coagulopathy; fibrinolysis; activated clotting time (ACT).

[1]*The Burn Center, Department of Surgery, MedStar Washington Hospital Center, Washington, DC 20010, USA;* [2]*Firefighters' Burn and Surgical Research Laboratory, MedStar Health Research Institute, Washington, DC 20010, USA;* [3]*Research Directorate, U.S. Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234, USA;* [4]*Department of Epidemiology and Biostatistics, University of Texas Tyler School of Medicine, Tyler, TX 75708, USA;* [5]*Department of Biochemistry, Georgetown University, Washington, DC 20057, USA;* [6]*Department of Biochemistry, College of Medicine, University of Vermont, Colchester, VT 05405, USA;* [7]*Department of Surgery, Georgetown University, Washington, DC 20057, USA;* [8]*Combat Casualty Care and Operational Medicine Directorate, Naval Medical Research Unit San Antonio, JBSA Fort Sam Houston, TX 78234, USA;* [9]*Department of Surgery, Uniformed Services University of Health Sciences, Bethesda, MD 20814, USA*

†Contributors of the SYSCOT Study Group are as follows: Maria-Cristina Bravo, PhD; Kathleen E. Brummel-Ziedins, PhD; Rachael A Callcut, MD; Mitchell J. Cohen, MD; Kalev Freeman, MD, PhD; Aarti Gautam, PhD; Rasha Hammamieh, PhD; Marti Jett, PhD; Melissa M. McLawhorn, RN, BSN; Lauren T. Moffatt, PhD; Linda R. Petzold, PhD; Anthony E. Pusateri, PhD; Jeffrey W. Shupp, MD; Jeffrey D. Varner, PhD.

Author Contributions: Anthony E Pusateri (Conceptualization: Lead; Data curation: Equal; Formal analysis: Supporting; Funding acquisition: Supporting; Methodology: Supporting; Project administration: Supporting; Writing – original draft: Supporting; Writing – review & editing: Lead), John W Keyloun (Formal analysis: Supporting; Investigation: Equal; Methodology: Supporting; Writing – original draft: Equal; Writing – review & editing: Supporting), Tuan D Le (Conceptualization: Supporting; Data curation: Equal; Formal analysis: Lead; Writing – original draft: Equal; Writing – review & editing: Supporting), Lauren T Moffatt (Data curation: Supporting; Funding acquisition: Equal; Investigation: Equal; Methodology: Supporting; Project administration: Lead; Resources: Supporting; Supervision: Equal; Writing – original draft: Supporting), Thomas Orfeo (Conceptualization: Supporting; Investigation: Supporting; Project administration: Supporting; Writing – original draft: Supporting), Melissa M McLawhorn (Data curation: Supporting; Investigation: Supporting; Methodology: Equal; Project administration: Supporting; Resources: Supporting; Supervision: Supporting; Writing – original draft: Supporting), Jeffrey W Shupp (Conceptualization: Supporting; Data curation: Supporting; Funding acquisition: Lead; Investigation: Lead; Project administration: Equal; Resources: Equal; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Supporting), Linda R Petzold (Data curation: Supporting; Funding acquisition: Supporting; Investigation: Supporting; Writing – original draft: Supporting), Jeffrey D Varner (Conceptualization: Supporting; Data curation: Supporting; Funding acquisition: Supporting; Writing – original draft: Supporting), Maria C Bravo (Conceptualization: Supporting; Data curation: Supporting; Funding acquisition: Supporting; Writing – original draft: Supporting), Kalev Freeman (Funding acquisition: Supporting; Investigation: Supporting; Writing – original draft: Supporting), Aarti Gautum (Data curation: Supporting; Investigation: Supporting; Writing – original draft: Supporting), Shawn Tejiram (Writing – original draft: Supporting), Mitchell J Cohen (Conceptualization: Supporting; Investigation: Supporting; Methodology: Supporting; Project administration: Supporting; Resources: Supporting; Visualization: Supporting), Kathleen E Brummel-Ziedens (Conceptualization: Supporting; Funding acquisition: Equal; Methodology: Equal; Resources: Supporting; Writing – review & editing: Supporting)

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[*]Address correspondence to A.E.P. (email: acpusateri@gmail.com)

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INTRODUCTION

During the early postburn period, approximately 10–15% of thermally injured patients develop acute burn-induced coagulopathy (hypo-coagulable state), which has been associated with increased resuscitation requirements and increased mortality.[1–3] Coagulopathy in these patients has been documented by standard plasma-based coagulation assays, such as PT, INR, and aPTT, and by thromboelastography (TEG). Additionally, abnormal fibrinolytic function (hypo- or hyperfibrinolysis as detected by TEG) may develop during this period and has also been associated with increased mortality.[4] Acute traumatic coagulopathy and early fibrinolytic dysfunction have been well-documented in patients with nonburn trauma.[5,6] Advances in trauma care have targeted early diagnosis and treatment of acute traumatic coagulopathy with Viscoelastic Assays (VEAs) as an important component of treatment algorithms.[7] TEG is applied in many surgical fields, such as trauma, cardiac, hepatobiliary, and burn.[8–13] TEG has been used more frequently during the excision and grafting surgery period rather than the early resuscitative phase in patients with burn injury.

While standard plasma-based coagulation assays are highly standardized and universal in the hospital setting, TEG is less standardized and is less widely available. There are several modalities of TEG but the most common formats are native-TEG (nTEG), kaolin-TEG (kTEG), and rapid-TEG (rTEG). In nTEG, only calcium is added to initiate clotting, resulting in a slow, spontaneous activation of the intrinsic pathway by contact with the plastic surface of the TEG cup.[14] In kTEG, kaolin is added along with calcium to strongly trigger the intrinsic pathway via factor XII.[15] In addition to calcium and kaolin, rTEG includes tissue factor, which initiates the extrinsic coagulation pathway through factor VII, resulting in the most rapid clot development.[16] Previous studies have demonstrated that there is variable agreement between TEG methods for each parameter (R, α-angle, MA, and LY30).[15,17,18] Studies to date have involved single timepoint samples from normal volunteers and a limited number of patients. However, no study has examined the relative performance of these assays in patients with burn injury or investigated how the choice of an assay may impact clinical determinations of coagulation status. Based on reagent choice, TEG assays may vary in how parameters are associated with injury characteristics and outcomes, such that choice of TEG assay could differentially influence clinical decision-making.[19] We hypothesized that agreement among TEG assays would be low for most parameters, and that this could result in different determinations with respect to patient coagulation or fibrinolytic status. This study compared values for different TEG assays in a cohort of patients with burn injury, examined the ability of each TEG assay to detect differences in coagulation and fibrinolytic function based on patient subgroups, and characterized the level of agreement among the different TEG assays.

METHODS

Patients

The Institutional Review Board of MedStar Health Research Institute and the Human Research Protections Office of the US Army Medical Research and Development Command approved this research. The requirement to obtain advanced written informed consent for emergency research was waived in accordance with US Code of Federal Regulations Title 21, Part 50—Protection of Human Subjects, Subpart B—Informed Consent in Human Subjects and Section 50.24—Exception from Informed Consent Requirement for Emergency Research. This study was conducted as part of the larger multicenter Systems Biology Coagulopathy of Trauma (SYSCOT) Research Program.[20] Thermally injured patients presenting to the MedStar Washington Hospital Burn Center, an American Burn Association verified regional burn center, between 2013 and 2017 were enrolled. Inclusion criteria included ≥18 years old and presenting no more than 4 h after injury. Exclusion criteria included chemical burn injuries, actively taking anticoagulant medications, not fluent in either English or Spanish, or otherwise deemed ineligible for inclusion based on preexisting conditions, such as Von Willebrand disease or other hemostatic disorder. Some of the research data on these patients has been reported previously.[4]

Study design

Standardized timepoints for blood collection were scheduled at admission (hour 0; H0) and hours 2, 4, 8, 12, 24, every 12 h until hour 168 (day 7) and days 14 and 21. rTEG, kTEG, and nTEG assays were run simultaneously. For the H0 sample only, platelet count, PT, INR, and aPTT were determined. For all time points, TEG was performed. For TEG, 2.7 mL blood was collected at each time point, while a total of up to 20 mL was collected as part of a larger study.[20] No TEG data were used for clinical decision-making, and treating clinicians were blinded to the TEG results. Larger burns are associated with acute burn-induced coagulopathy.[2,3] Therefore, coagulation status was characterized for patient cohorts with larger versus smaller burns. We performed a similar characterization for patients based on 28-day in-hospital mortality. TEG findings were compared to results based on standard plasma-based coagulation assays. Next, TEG assays were examined with respect to detection of abnormal fibrinolytic function using both manufacturer ranges and published cutoffs, as described below.[4,21] Finally, the level of agreement among rTEG, kTEG, and nTEG assay results was determined.

Thromboelastography

Whole blood specimens were collected at the designated timepoints into sodium citrate 3.2% (0.109 mol/L; nine volumes blood to one volume anticoagulant) tubes. The institution's perfusion services department performed rTEG, kTEG, and nTEG assays using the TEG 5000 Hemostasis Analyzer according to the manufacturer's instructions (Haemonetics Corp., Braintree, MA). The following four parameters were analyzed: R, α-angle, MA, and LY30. Normal ranges for each TEG assay parameter were established by the manufacturer (Table 1). R-time is a measurement of the time it takes from the initiation of the assay until the first detection of a clot and serves as a functional measure of the balance of pro- and anti-coagulant processes that control the onset of coagulation. The α-angle reflects the speed of clot formation and strength of the thrombin burst. MA is a measure of the maximum strength of the platelet/fibrin clot. LY30 is a functional measure of endogenous fibrinolytic activity, defined as the percentage of clot lysis 30 min

Table 1. Manufacturer's Normal Ranges for TEG Parameters

	Assay		
Parameter	**nTEG**	**kTEG**	**rTEG**
ACT, s	–	–	70–120
R, min	9–27	2–8	0–1
α-angle, degrees	22–58	55–78	66–82
MA, mm	44–64	51–69	54–72
LY30, %	0–8	0–8	0–8

Abbreviations: ACT, Activated clotting time; kTEG, kaolin TEG; LY30, clot lysis at 30 minutes; nTEG, native TEG; MA, maximum amplitude; R, reaction time; rTEG, rapid TEG; TEG, thromboelastography.

after MA. Activated clotting time (ACT) is an additional TEG parameter that measures clot initiation (available for rTEG only). Results of TEG can be influenced by both patient characteristics (eg disease state, oral anticoagulants) and pre-analytical variables (eg difficult phlebotomy).[22,23] To minimize the impact of these factors, potential differences among different TEG activators were assessed using identical aliquots from the same patient samples. These assays were run by a clinical laboratory which runs TEG for patient care. Some assays were not completed due to logistic constraints, as clinical samples took priority over research samples.

Categorizing coagulation and fibrinolytic function with TEG

To assess coagulation, ACT, R, α-angle, and MA were rated normal or abnormal based on manufacturer's reference ranges. A cutoff of TEG α-angle ≤60 °C was also applied, based on a report that α-angle ≤60 °C was associated with increased mortality and fluid requirements in burn patients.[1] Fibrinolytic function was examined based on manufacturer's reference ranges (Table 1) and based on fibrinolytic phenotypes.[21] The hypofibrinolytic phenotype (also called fibrinolytic shutdown; SD) was defined as LY30 < 0.6%. The normal/physiologic (PHYS) phenotype was defined as LY30 0.6%–7.7%. The hyperfibrinolytic (HF) phenotype was defined as LY30 > 7.7%.[21]

Clinical data

Clinical data were prospectively collected from the medical records including demographics, injury characteristics, laboratory, physiologic measures, clinical management, and outcomes. Admission coagulation assay data (PT/INR and aPTT) were used to determine the incidence of acute burn-induced coagulopathy using published definitions (INR > 1.2 or aPTT > 45 s).[2] Following the admission blood samples, patients received VTE chemoprophylaxis (enoxaparin or heparin sulfate) upon admission and daily unless contraindicated due to bleeding diathesis.

Statistical analysis

Continuous variables were tested for normality, expressed as medians and interquartile ranges (IQRs), and were compared for differences between burn size groups or discharge status using Mann-Whitney *U* test. Patients were categorized by burn severity (<40% or ≥40% TBSA), in-hospital mortality, and fibrinolytic phenotypes. Categorical variables were presented as frequencies and percentages and tested for association with the fibrinolytic phenotypes using chi-square test. TEG parameters were compared among assays as both continuous and categorical variables. Continuous data included: Age (years), BMI, Time from arrival on scene to 1st blood draw (minutes), %TBSA, Baux score, Glasgow Coma Score, PT (seconds), aPTT (seconds), INR, Platelet count ($\times 10^3$/ul), Length of Stay (days), TEG ACT (seconds), TEG R (minutes), TEG α-angle (degrees), TEG MA (mm), and TEG LY30 (%). Categorical data included: Male/Female, Ethnicity, Inhalation Injury, and Mortality. In addition, cutoff definitions for: α-angle ≤60, Acute Burn-induced Coagulopathy, Fibrinolytic Phenotype, Burn Severity Category, and classifications based on manufacturer's reference ranges were treated as categorical data. Concordance correlation coefficients were calculated at admission (H0, the single timepoint with the greatest number of observations) and pooled across the 21-day sampling period (providing the maximum total number of observations) to assess the level of agreement among assays for each parameter (R, α-angle, MA, LY30). Cohen's Kappa Coefficient (k) was calculated to investigate interclass reliability among TEG assays using the symmetry test. Logistic regression for computing the odds ratio was also used to determine the association of admission HF and delayed SD (SD at hour 4) with mortality in burn patients based on prior work demonstrating that these phenomena were associated with mortality in burn patients.[4] Logistic regression was also used to determine the association of manufacturer's range hyperfibrinolysis with mortality. Statistical significance was set at the 2-sided *P*-value of .05. All data were analyzed using SAS, version 9.4 (SAS Institute Inc.).

RESULTS

Demographics and injury characteristics

Of 158 thermally injured patients enrolled in this study, 121 patients who met inclusion criteria were analyzed (Figure 1). A description of patient demographics and injury characteristics is presented in Table 2. To identify clinically relevant associations between assay parameter results, patients were categorized by burn size (≥40% TBSA, n = 23) and 28-day in-hospital mortality (Dead, n = 21). Patients with severe burns (≥40% TBSA) and those who died were older, had more concomitant inhalation injury, higher Baux scores, and lower admission Glasgow coma scores. There was a higher mortality rate among severe burns, and those who died had shorter hospital length of stay (Table 2).

TEG assay parameters, fibrinolytic phenotypes, and clinical outcomes

At admission, severe burn injury (≥40% TBSA) was associated with lower median α-angle on rTEG (P = .03). There were also lower median MA values in severe burns on rTEG (P = .02) and kTEG (P = .01; Table 3). MA was lower among

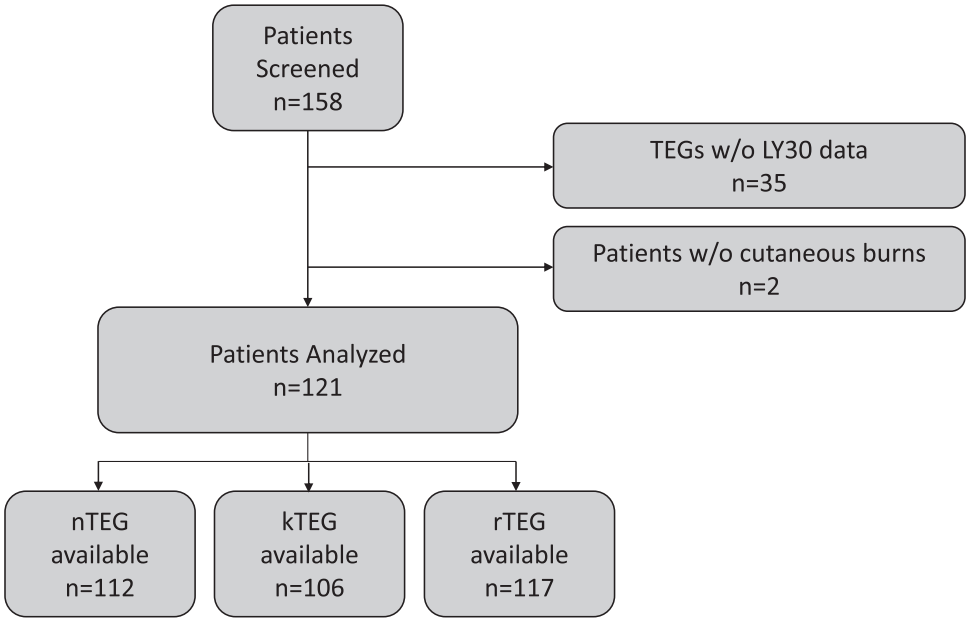

Figure 1. Flow Chart of Cohort Included in This Study

Table 2. Patient Demographic Characteristics and Admission Laboratory Data

Characteristic	Total (*n* = 121)	<40% TBSA (*n* = 98)	≥40% TBSA (*n* = 23)	*P*-value	Alive (*n* = 100)	Dead (*n* = 21)	*P*-value
Male, no. (%)	84 (69.4)	67 (67.7)	18 (78.2)	.32	68 (68.0)	16 (76.2)	.46
Age, yr	40 (29–57)	39 (27–52)	49 (36–63)	.01	38 (27–50)	60 (40–68)	.0003
Ethnicity, No. (%)				.06			.21
Caucasian	42 (34)	36 (36)	6 (26)		36 (36.0)	6 (28.6)	
African American	47 (38)	38 (38)	9 (39)		36 (36.0)	9 (42.9)	
Hispanic	11 (9)	11 (11)	0 (0)		12 (12.0)	0 (0.0)	
Other	22 (18)	14 (14)	8 (35)		16 (16.0)	6 (28.5)	
BMI	26.6 (23.7–30.5)	26.8 (23.4–31.1)	26.1 (23.8–27.3)	.45	27.0 (23.7–31.1)	25.8 (23.7–27.0)	0.12
Time arrival on scene to first blood draw, min	104 (76–163)	97 (74–160)	107 (90–194)	.13	105 (79–170)	107 (75–150)	.77
Total %TBSA	12.7 (6.0–28.5)	10.3 (5.0–18.5)	60.7 (46.5–90.0)	<.0001	10.8 (5.0–20.3)	60.8 (46.0–90.0)	<.0001
Inhalation Injury, No. (%)	29 (24.1)	14 (14.3)	15 (65.2)	<.0001	17 (17.0)	12 (63.2)	<.0001
Admission Baux score	60.0 (40.2–82.0)	53.5 (37.6–69.0)	110.0 (92.0–151.5)	<.0001	54.0 (38.0–69.8)	104.0 (91.3–151.3)	<.0001
Admission GCS	15 (13.7–15)	15 (15–15)	7 (3–15)	<.0001	15 (15–15)	3 (3–15)	<.0001
PT, s	13.8 (13.2–14.7)	13.7 (13.1–14.3)	14.8 (14.4–15.5)	.0003	13.7 (13.1–14.3)	14.8 (14.3–15.8)	.0002
aPTT, s	28.1 (25.8–30.4)	27.6 (25.5–29.7)	30.6 (28.7–35.8)	.0006	27.6 (25.5–29.7)	30.4 (28.7–36.3)	.0013
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.2–1.3)	.0006	1.1 (1.0–1.2)	1.2 (1.2–1.3)	.0012
Platelet count (x10^3/ul)	259 (210–300)	240 (208–285)	379 (268–552)	<.0001	246 (210–285)	356 (264–552)	.0027
Coagulopathy, No. (%)	14/106 (13.2)	8/89 (9.0)	6/17 (35.3)	.0097	8/90 (8.9)	6/16 (37.5)	.0068
Length of Stay, days	8.5 (2–18)	9 (3–18)	3 (1–35)	.31	11 (5–21)	2 (1–13)	.0062
Mortality, No. (%)	21 (17.4)	5 (5.1)	16 (69.6)	<.0001	–	–	–

BMI, body mass index; GCS, Glasgow coma scale; IQR, interquartile ranges; TBSA, total body surface area.
Continuous data are presented as median (IQR) unless otherwise indicated. Statistical comparisons are between patients with large vs small burns and between patients who died versus survived. *P*-value was calculated using Mann–Whitney *U* test or chi-square or Fisher's exact test where appropriate. Coagulopathy was defined as an INR > 1.2 and/or aPTT > 45 s at admission.[2] PT, aPTT, INR, Platelet count, and coagulopathy data are based on admission blood samples. Local clinical laboratory normal reference ranges: PT, 11.8–14.6 s; aPTT, 23.4–36.2 s; platelets, 145–400 × 10^3/μl.

patients who died for each of the TEG activators, while no other differences were observed (Table 4). As shown in Tables 5 and 6, the percentage of patients with rTEG α-angle ≤60° was statistically higher in patients with larger burns (Table 5) and in patients who died (Table 6; $P < .0001$). Statistical differences were not observed for either nTEG or kTEG, although the numerical trends were similar. Based on logistic regression analysis, hyperfibrinolysis (based on manufacturer

Table 3. Admission TEG Parameters and Burn Size

	Total (n = 121)	<40% TBSA (n = 98)	≥40% TBSA (n = 23)	*P*-value
nTEG at H0				
R, min	4.8 (3.3–6.2)	4.8 (3.2–6.3)	4.5 (3.8–5.8)	.30
α-Angle, degrees	68.3 (64.8–72.5)	68.5 (66.1–72.7)	66.9 (60.5–71.4)	.06
MA, mm	59.1 (54.7–63.6)	59.6 (55.6–64.1)	58.9 (45.8–61.5)	.15
LY30, %	1.2 (0.2–4.3)	1.3 (0.1–3.8)	1.1 (0.2–5.8)	.73
kTEG at H0				
R, min	3.9 (3.0–4.5)	4.0 (2.9–4.5)	3.8 (3.3–4.4)	.83
α-Angle, degrees	71.5 (67.9–74.6)	71.7 (68.6–74.7)	69.9 (64.0–74.5)	.19
MA, mm	59.2 (55.7–64.2)	59.5 (55.9–65.3)	56.0 (47.7–61.7)	.01
LY30, %	2.4 (0.6–5.2)	2.4 (0.9–4.9)	2.7 (0.0–7.0)	.97
rTEG at H0				
ACT, s	121 (105–136)	121 (105–128)	121 (105–183)	.20
R, min	0.8 (0.6–0.9)	0.8 (0.6–0.82)	0.8 (0.6–1.4)	.54
α-Angle, degrees	73.9 (69.4–77.2)	74.1 (70.7–77.2)	66.4 (54.4–76.1)	.03
MA, mm	61.8 (56.5–65.1)	62.0 (58.1–65.9)	56.7 (44.0–64.0)	.02
LY30, %	1.5 (0.3–3.3)	1.5 (0.4–3.4)	0.7 (0.0–8.3)	.37

ACT, Activated clotting time; IQR, interquartile range; kTEG, kaolin TEG; LY30, clot lysis at 30 minutes; MA, maximum amplitude; nTEG, native TEG; R, reaction time; rTEG, rapid TEG; TEG, thromboelastography.
Data are presented as median (interquartile ranges). *P*-values were calculated using Mann–Whitney test.

Table 4. Admission TEG Parameters and Survival

	Total (n = 121)	Alive (n = 100)	Dead (n = 21)	*P*-value
nTEG at H0				
R, min	4.8 (3.3–6.2)	4.8 (3.4–6.2)	3.9 (2.6–5.8)	.20
α-Angle, degrees	68.3 (64.8–72.5)	68.3 (65.7–72.6)	67.4 (62.0–71.7)	.33
MA, mm	59.1 (54.7–63.6)	59.6 (56.0–64.0)	55.5 (44.3–61.5)	.04
LY30, %	1.15 (0.2–4.3)	1.2 (0.2–3.8)	2.0 (0.2–5.5)	.62
kTEG at H0				
R, min	3.9 (3.0–4.5)	4.0 (3.0–4.5)	3.5 (3.2–4.4)	.70
α-Angle, degrees	71.5 (67.9–74.6)	72.0 (68.6–74.7)	70.4 (64.0–74.0)	.15
MA, mm	59.2 (55.7–64.2)	59.5 (56.0–65.2)	55.7 (47.7–61.5)	.02
LY30, %	2.4 (0.6–5.2)	2.5 (0.9–5.1)	1.4 (0.1–7.0)	.75
rTEG at H0				
ACT, s	121 (105–136)	121 (105–136)	113 (97–128)	.43
R, min	0.8 (0.6–0.9)	0.8 (0.6–0.9)	0.7 (0.6–0.8)	.47
α-Angle, degrees	73.9 (69.4–77.2)	73.6 (70.3–77.2)	74.2 (54.4–75.9)	.10
MA, mm	61.8 (56.5–65.1)	62.3 (57.8–65.5)	56.7 (44.0–60.4)	.003
LY30, %	1.5 (0.3–3.3)	1.6 (0.4–3.1)	1.3 (0.2–8.3)	.94

Data are presented as median (interquartile ranges). *P*-values were calculated using Mann–Whitney test.

definitions) was associated with mortality on rTEG only (Table 7; P = .003). The association of fibrinolytic dysfunction and mortality was also examined based on the published fibrinolytic phenotypes, HF, PHYS, and SD.[21] The proportion of patients with abnormal fibrinolytic phenotypes (HF or SD) was greater in severe burns (Figure 2C; P = .0003) and in patients who died (Figure 2F; P = .03) on rTEG only. At admission, the HF phenotype was associated with mortality on rTEG (P = .001) but not on nTEG and kTEG (Table 7). At 4 h post-admission, LY30 data were available for 80, 78, and 86 patients for nTEG, kTEG, and rTEG. For nTEG, 37.5%, 50.0%, and 12.5% were SD, PHYS, and HF. For kTEG, 32.1%, 55.1%, and 12.8% were SD, PHYS, and HF. For rTEG, 44.2%, 50.0%, and 5.8% were SD, PHYS, and HF. When investigating four-hour delayed SD and likelihood of mortality, delayed SD was associated with a greater odds of mortality using nTEG (P = .02) and rTEG (P = .005) but not kTEG (Table 7).

Admission TEG parameters in burn patients

The manufacturer's normal ranges are shown in Table 1. When patient admission TEG assay parameters were compared for all patients (Table 8), R-time and α-angle

Table 5. TEG Parameters and Burn Size

	Total (n = 121)	<40% TBSA (n = 98)	≥40% TBSA (n = 23)	*P*-value
nTEG at H0				
% with α-Angle ≤60°	12/111 (10.8)	7/88 (8.0)	5/23 (21.7)	.12
kTEG at H0				
% with α-Angle ≤60°	7/105 (6.7)	4/86 (4.7)	3/19 (15.8)	.11
rTEG at H0				
% with α-Angle ≤60°	12/115 (10.4)	3/92 (3.3)	9/23 (39.1)	<.0001

kTEG, kaolin-TEG; nTEG, native-TEG; rTEG, rapid TEG; TEG, thromboelastography.
P-values were calculated using chi-square test.

Table 6. TEG Parameters and Survival

	Total (n = 121)	Alive (n = 100)	Dead (n = 21)	*P*-value
nTEG at H0				
% with α-Angle ≤60°	12/111 (10.8)	8/90 (8.9)	4/21 (19.1)	.24
kTEG at H0				
% with α-Angle ≤60°	7/105 (6.7)	4/88 (4.6)	3/17 (17.7)	.82
rTEG at H0				
% with α-Angle ≤60°	12/115 (10.4)	4/94 (4.3)	8/21 (38.1)	< .0001

kTEG, kaolin-TEG; nTEG, native-TEG; rTEG, rapid TEG; TEG, thromboelastography.
P-values were calculated using chi-square test.

Table 7. Likelihood of Mortality Based on Manufacturer Fibrinolytic Normal Ranges and Published Fibrinolytic Phenotypes

	Odds ratio (95% CI)	*P*-value
nTEG-LY30		
Manufacturer's range admission hyperfibrinolysis vs normal	1.71 (0.41–7.08)	.46
Admission HF vs PHYS phenotype	1.61 (0.37–6.91)	.52
Delayed SD vs PHYS phenotype	6.91 (1.35–35.48)	.02
kTEG–LY30		
Manufacturer's range admission hyperfibrinolysis vs normal	1.34 (0.33–5.37)	.68
Admission HF vs PHYS phenotype	1.65 (0.38–7.22)	.50
Delayed SD vs PHYS phenotype	1.62 (0.48–5.52)	.44
rTEG-LY30		
Manufacturer's range admission hyperfibrinolysis vs normal	7.04 (1.91–26.01)	.003
Admission HF vs PHYS phenotype	10.45 (2.54–43.31)	.001
Delayed SD vs PHYS phenotype	9.46 (1.96–45.73)	.005

Data were analyzed by logistic regression. Definitions for manufacturer's range: normal, LY30 ≤ 8%; hyperfibrinolysis, LY30 > 8%. Definitions for fibrinolytic phenotypes: SD, LY30 < 0.6%; PHYS, LY30 0.6–7.7%; HF, LY30 > 7.7%.[21]

parameters were significantly different between nTEG and both kTEG and rTEG. R-time median values for nTEG were longer than for kTEG (P < .0001) and rTEG (P < .0001). nTEG α-angle median values were lower than for kTEG (P = .0005) and rTEG (P < .0001), while kTEG was also lower than rTEG (P = .02). MA values were lower on nTEG when compared to rTEG (P = .02). Median values for burn patient TEG assay parameters mostly fell within the manufacturer's normal ranges. Notably, the following parameters fell outside manufacturer's ranges: rTEG ACT (higher) and nTEG R-time (lower) and α-angle (higher) (Table 8).

Level of agreement (Rc) and interclass reliability (κ) between TEG assays

Concordance correlation coefficients (Table 9) for all parameters were highest overall between nTEG and kTEG for R-time, α-angle, MA, and LY30 and lowest between nTEG and rTEG for R-time, α-angle, MA, and LY30. Agreement was poor between rTEG and nTEG or kTEG for R-time. Overall, there was lowest agreement between TEG assays on R-time and α-angle and moderate to strong agreement on MA and LY30. For LY30, agreement between assays was highest on admission, and most consistent across all sampling times between nTEG and kTEG assays.

TEG parameters were categorized as normal or abnormal based on the manufacturer's reference range specific to each assay. Admission interclass reliability (Cohen's Kappa) was lowest for R-time and α-angle and highest for MA and LY30. Over the 21-day study period, interclass reliability generally remained low for all parameters. nTEG and rTEG had the lowest interclass reliability across all parameters and timepoints (Table 10).

DISCUSSION

rTEG appeared most sensitive in parameter-specific associations with injury severity, abnormal fibrinolysis, and mortality, and was the only assay that detected associations between both the

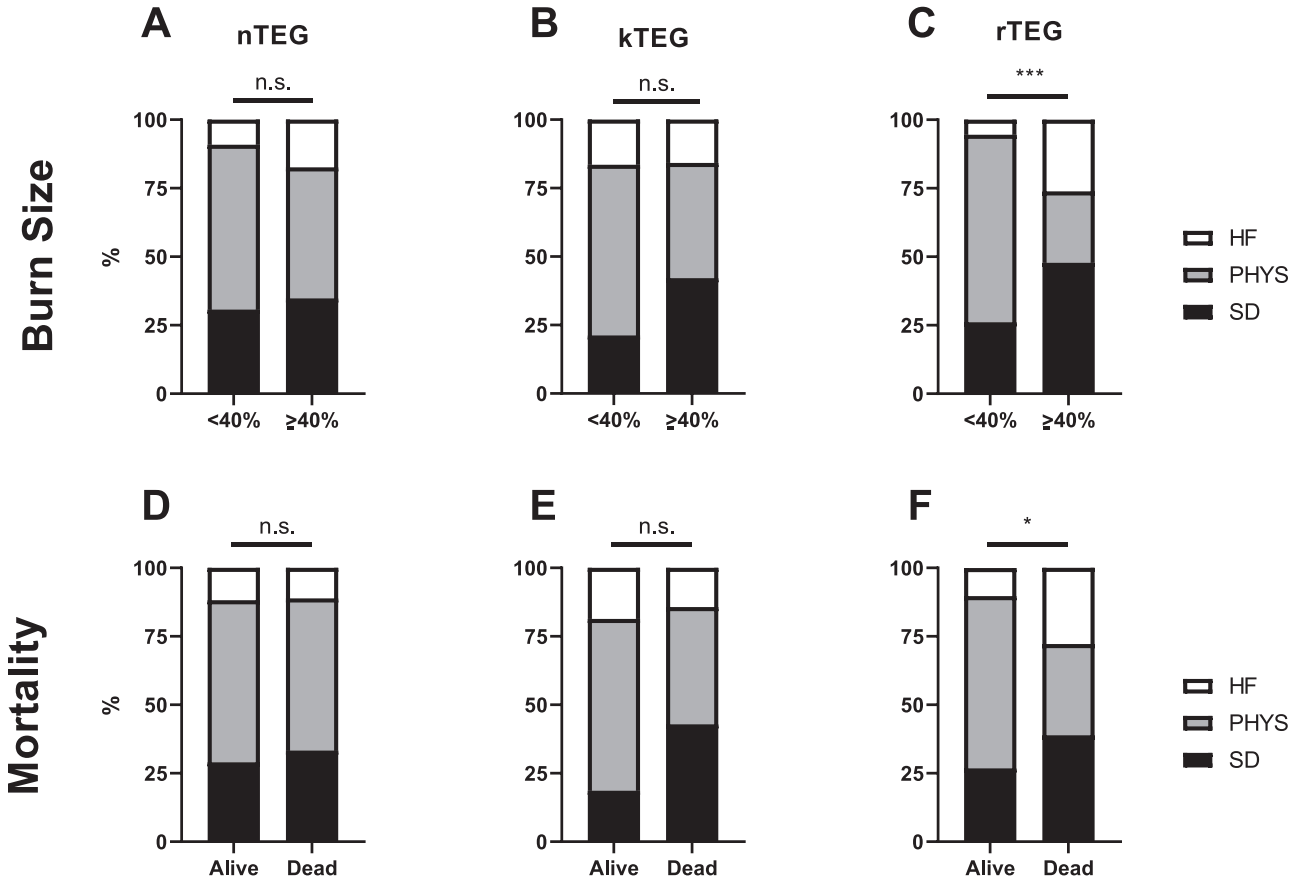

Figure 2. Proportion of Patients Exhibiting Fibrinolytic Phenotypes (SD, PHYS, HF) by Burn Size (≥40% TBSA; Top Row) and Mortality (Bottom Row) Compared Using the Chi-Square Test. n.s Denotes Not Statistically Significant; **P* < .05, ****P* < .0001.

Table 8. Admission TEG Parameters

Parameter	nTEG (*n* = 112)	kTEG (*n* = 106)	rTEG (*n* = 117)
ACT, s	–	–	121 (105–136)
R, min	4.8 (3.3–6.2)*†	3.8 (3.0–4.5)*‡	0.8 (0.6–0.9)†‡
α-Angle, degrees	68.3 (64.8–72.5)*†	71.5 (67.9–74.6)*‡	73.9 (69.4–77.2)†‡
MA, mm	59.1 (54.7–63.6)†	59.2 (55.7–64.2)	61.8 (56.4–65.1)†
LY30, %	1.1 (0.2–4.3)	2.4 (0.6–5.2)	1.5 (0.3–3.3)

All values shown are median (interquartile range; IQR) for the TEG parameters at admission. ACT, Activated clotting time; IQR, interquartile range; kTEG, kaolin TEG; LY30, clot lysis at 30 minutes; MA, maximum amplitude; nTEG, native TEG; R, reaction time; rTEG, rapid TEG; TEG, thromboelastography.
Statistical significance for within row comparisons are denoted as follows: (*) nTEG vs kTEG; (†) nTEG vs rTEG; (‡) kTEG vs rTEG, calculated using Mann–Whitney *U* test. For *R*, all differences *P* < .0001. For α-angle, nTEG vs kTEG, *P* = .0005, nTEG vs rTEG, *P* < .0001, and kTEG vs rTEG, *P* = .02. For MA, nTEG vs rTEG, *P* = .02.

HF and SD fibrinolytic phenotypes and mortality. Agreement among TEG assays was low to moderate for most parameters. The rTEG, kTEG, and nTEG methods differed in ability to differentiate between patient populations with higher versus lower incidences of coagulopathy or fibrinolytic dysfunction. These findings support our initial hypotheses and suggest that selection of TEG method may influence clinical interpretation.

We examined the ability of TEG methods to differentiate between patient populations expected to have higher versus lower incidences of coagulopathy.[1–3] Acute burn-induced coagulopathy (defined by standard plasma-based assays) was present at admission in 13.2% (*n* = 14) of patients, and was more common among patients with larger burns and among those who died, as previously observed.[2,3] Admission platelet counts were higher both in the patient subgroup with larger burns and in the patient subgroup who died by 28 days. The observed platelet counts are similar to those previously reported at the time of admission in patients with thermal injury.[24,25] Although there were differences in platelet counts between the patient cohorts shown in Table 2, the medians

Table 9. Concordance Correlation Coefficient (Rc) Among TEG on Admission (H0) and for Data Pooled over 21 Days

TEG parameter	nTEG and kTEG	nTEG and rTEG	kTEG and rTEG
	Rc (95% CI)	Rc (95% CI)	Rc (95% CI)
Reaction time (*R*)			
H0	0.56 (0.47 to 0.63)	0.00 (−0.06 to 0.07)	0.01 (−0.03 to 0.04)
Pooled thru Day 21	0.35 (0.33 to 0.37)	0.02 (0.01 to 0.06)	0.05 (0.02 to 0.08)
Speed of clot formation (α-angle)			
H0	0.55 (0.40 to 0.67)	0.40 (0.24 to 0.54)	0.69 (0.57 to 0.78)
Pooled thru Day 21	0.55 (0.50 to −0.59)	0.22 (0.18 to 0.25)	0.50 (0.46 to 0.55)
Maximum amplitude (MA)			
H0	0.81 (0.73 to 0.87)	0.70 (0.60 to 0.79)	0.67 (0.55 to 0.77)
Pooled thru Day 21	0.82 (0.80 to 0.84)	0.65 (0.62 to 0.69)	0.75 (0.72 to 0.77)
Clot lysis at 30 min (LY30)			
H0	0.72 (0.61 to 0.80)	0.92 (0.89 to 0.95)	0.93 (0.90 to 0.95)
Pooled thru Day 21	0.71 (0.68 to 0.74)	0.63 (0.60 to 0.67)	0.69 (0.65 to 0.72)

H0, admission; kTEG, kaolin-TEG; nTEG, native-TEG; rTEG, rapid TEG; TEG, thromboelastography.
Data are presented as Concordance Correlation Coefficients (Rc) with 95% confidence intervals.

Table 10. Interclass Reliability (κ) among TEG on Admission (H0) and for Data Pooled over 21 Days

	nTEG and kTEG κ (95% CI)	nTEG and rTEG κ (95% CI)	kTEG and rTEG κ (95% CI)
Reaction time (*R*)			
H0	−0.02 (−0.06 to 0.02)	0.01 (0.00 to 0.02)	−0.07 (−0.12 to −0.03)
Pooled thru Day 21	−0.02 (−0.04 to −0.01)	−0.03 (−0.05 to −0.01)	0.09 (0.01 to 0.16)
Speed of clot formation (α–angle)			
H0	−0.03 (−0.09 to 0.03)	−0.06 (−0.13 to 0.02)	0.17 (−0.06 to 0.39)
Pooled thru Day 21	−0.01 (−0.03 to 0.01)	−0.03 (−0.05 to −0.01)	0.32 (0.24 to 0.40)
Maximum amplitude (MA)			
H0	0.51 (0.31 to 0.70)	0.22 (0.03 to 0.42)	0.44 (0.22 to 0.66)
Pooled thru Day 21	0.43 (0.38 to 0.48)	0.31 (0.26 to 0.36)	0.44 (0.39 to 0.50)
Clot lysis at 30 min (LY30)			
H0	0.49 (0.21 to 0.76)	0.29 (0.02 to 0.57)	0.44 (0.16 to 0.70)
Pooled thru Day 21	0.31 (0.21 to 0.42)	0.26 (0.15 to 0.37)	0.22 (0.11 to 0.33)

H0, admission; kTEG, kaolin-TEG; nTEG, native-TEG; rTEG, rapid TEG; TEG, thromboelastography.
Data are presented as Cohen's Kappa (κ) with 95% confidence intervals.

for all groups were within the normal reference ranges at our institution. Huang et al., 2019 found that platelet counts in severely burned patients were higher at admission in the subgroup of patients that died by 30 days (305.91 ± 165.82 vs 223.42 ± 85.21 × 109/L, $P < .01$).[24] Platelet counts in both survivors and nonsurvivors did not decline until after the first 24 h following injury. The authors proposed that the later decline was the result of dilution due to fluid resuscitation and activation of coagulation at burn sites and elsewhere. These findings are similar to our findings related to survival and nonsurvival. Subsequent declines in platelet counts after admission may also be related to the development of disseminated intravascular coagulation in some patients.[25] The reason for the observed higher admission platelet counts is not clear but may be due to greater initial intravascular fluid loss associated with larger burns.[26]

TEG initiated with different activators in these patient groups yielded different results. None of the TEG parameters were significantly different between large and small burn groups for nTEG. Using kTEG, a decreased MA was observed in the larger burn group, consistent with coagulopathy. Using rTEG, both α-angle and MA were reduced. The incidence of low α-angle (≤60 °C) was higher in patients with larger versus smaller burns only for rTEG. We found that MA was lower in patients who died versus those who lived for all of the TEG activators. The incidence of α-angle ≤60 °C was elevated in patients who died when using rTEG, consistent with the findings of Huzar et al.[1] However, low α-angle did not differ when kTEG or nTEG were used. Thalheimer et al. also reported different abilities of various TEG methods to distinguish between patient populations.[17] Taken together, data indicate that rTEG consistently detected differences relevant to coagulopathy, while nTEG or kTEG did not as clearly differentiate among patient subgroups.

Using rTEG, we have previously reported for the present burn patient population that HF at admission and SD at 4 h post-admission were each independently associated with mortality.[4] Similar relationships have been reported for nonburn trauma, both adult and pediatric.[27,28] In the present logistic regression analysis, HF at admission was associated with mortality using rTEG, but this association was not observed when using nTEG and kTEG (Table 7).

Delayed SD, defined as SD present at hour 4 after admission, was associated with mortality using rTEG and nTEG, but this relationship was not detected by kTEG (Table 7). When applying manufacturer's reference ranges to assess fibrinolytic dysfunction (ranges define only normal or hyperfibrinolysis), hyperfibrinolysis was also associated with mortality using rTEG but not nTEG or kTEG. Notably, hypofibrinolysis cannot be identified using manufacturer ranges because all include 0% LY30 within the normal range (Table 1).

TEG parameter data demonstrated discordance particularly when measuring clot initiation and propagation (R, α-angle; Table 9). The results from the three TEG assays reported here support previous work that demonstrated poor correlation (in absolute parameter values) between TEG assays in several disease states, and extends those observations to the burn population.[14,17,18] A similar pattern was observed when the TEG assay parameters were treated categorically, with very low interclass reliability among assays when R-time and α-angle were classified as normal or abnormal based on reference ranges specific to each activator (Table 10). There was greater agreement among activators on MA, which reflected maximum clot strength, and LY30, which reflected fibrinolytic activity. This agreement translated to better interclass reliability between assays for both MA and LY30 (Table 10). In general, however, the overall low level of agreement among assays ($\kappa \leq 0.5$) in identifying normal versus abnormal values suggested that TEG activator choice might differentially influence clinical decision-making, as clinicians use reference ranges to interpret results and guide treatment.

rTEG, kTEG, and nTEG differ only in the method of activating thrombin and coagulation. Rate of thrombin activation influences clot structure and cross-linking.[29,30] Therefore, it seems likely that the differing results of these methods is related to the different methods of activation. The rTEG activator stimulates both the intrinsic and extrinsic coagulation pathways, producing the most rapid, robust, and synchronized thrombin burst. This results in rapid platelet activation, fibrin polymerization, and cross-linking by Factor XIIIa. This may also result in greater binding of tissue plasminogen activator and plasminogen to platelet-bound fibrin, thereby also synchronizing fibrinolytic activation.[31] Therefore, rTEG provides an assay system that evaluates the blood sample under conditions of maximal stimulation. By stimulating only the intrinsic pathway, the kTEG activator is expected to induce a thrombin burst to initiate clotting, but to a lesser degree than rTEG. nTEG contains no activator other than calcium and is dependent on slow activation by contact with the plastic in the sample cup wall. This makes nTEG more susceptible to low levels of circulating native activators and interference by pre-analytical variables. It is possible that in systems with a less robust thrombin generation, such as nTEG, the clot is not maximally formed and the fibrinolytic system is not optimally activated. This may result in a less reliable response of the assay to coagulation changes related to burn injury status.

Strengths of the present study include the size of our patient population and the use of the three TEG assay procedures in parallel on identical patient blood samples. Our cohort is majority male with a median age of 40, which reflects national trends in burn injury epidemiology.[32–34] To date, this is the largest burn patient population for whom TEG is available and the first comparing different TEG methods on the same patient samples.

Limitations

There are several limitations of the current study. The data presented here come from a single-institution's experience and may not represent results of other centers. Additionally, the complete set of three TEG formats was not available for all patients due to workflow limitations. Nonetheless, most patients had complete sets, allowing for meaningful interpretation of the results. We used only published or manufacturer-provided cutoffs to interpret the various TEG data and did not attempt to develop optimized cutoffs for each method. It is possible that optimized cutoffs may improve nTEG and kTEG performance. Despite these limitations, we successfully show the discordant nature of TEG assay results in burn patients, highlighting the need for agreement among burn centers on the choice of assay and areas for further investigation.

CONCLUSION

Our results demonstrate discordance and poor interclass reliability among TEG assays when performed on identical citrated whole blood samples in parallel. Therefore, the choice of TEG activator may impact clinical decision-making. rTEG was the most sensitive assay in its parameter-specific associations with burn injury severity, suggesting slower (α-angle) and weaker (MA) clot formation in severely burned individuals on admission. With respect to fibrinolytic function, published literature definitions are useful but none of the current manufacturer-supplied ranges can be used to identify hypofibrinolysis. Furthermore, rTEG was the only assay that detected an association between both the HF and SD fibrinolytic phenotypes and mortality. Therefore, given its relative performance, rTEG may be the assay of choice for evaluating coagulation homeostasis in burn patients.

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