The rate of deep vein thrombosis doubles in trauma patients with hypercoagulable thromboelastography

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Author Disclosures

Martin Schreiber, MD – Consultant to Haemoscope
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Reviewer Disclosures

The reviewers have nothing to disclose.

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Submitted: February 9, 2017, Revised: May 12, 2017, Accepted: May 29, 2017, Published online: June 9, 2017.
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This study was presented at the 2016 meeting of the American College of Surgeons Committee on Trauma Region 9 Resident Paper Competition, December 3, 2016, in Los Angeles, California.
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DOI: 10.1097/TA.0000000000001618

BACKGROUND: Venous thromboembolism (VTE) in trauma can occur in patients at low risk. Conventional coagulation tests do not predict VTE. Studies investigating thromboelastography (TEG) for VTE risk are conflicting and have not included routine surveillance to detect deep vein thrombosis (DVT). We undertook a prospective study of TEG to evaluate its utility in predicting VTE.

METHODS: We conducted a prospective cohort study on all adult trauma patients admitted to our Level I trauma center from 2013 to 2015. TEG was performed immediately on arrival to the trauma bay. Hypercoagulable TEG was defined as reaction time (R) below, angle (α) above, or maximum amplitude (MA) above reference ranges. All patients received mechanical and/or pharmacologic prophylaxis and were followed up for DVT with our ultrasound surveillance protocol. The primary outcome was lower-extremity DVT. After bivariate analysis of variables related to DVT, those with p values of 0.100 or less were included for multivariate logistic regression.

RESULTS: A total of 983 patients were evaluated with TEG on admission; of these, 684 (69.6%) received at least one surveillance ultrasound during the index admission. Lower-extremity DVT was diagnosed in 99 (14.5%) patients. Hypercoagulability based on admission TEG occurred in 582 (85.1%) patients. The lower-extremity DVT rate was higher in patients with hypercoagulable TEG than in those without hypercoagulable TEG (15.6% vs. 8%; $p = 0.039$). Multivariate analysis showed hypercoagulable TEG remained associated with DVT after adjustment for relevant covariates available at admission, with an odds ratio of 2.41 (95% confidence interval, 1.11–5.24; $p = 0.026$).

CONCLUSION: Most trauma patients were hypercoagulable at admission and remained at risk of developing DVT. The rate of DVT doubled in patients with hypercoagulable TEG indices despite prophylaxis. Beyond its current clinical roles, TEG is useful for assessing DVT risk, particularly in patients otherwise perceived to be at low risk. (*J Trauma Acute Care Surg.* 2017;83: 413–419. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic study, level II.
KEY WORDS: Thromboelastography; trauma; deep vein thrombosis; venous thromboembolism.

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep venous thrombosis (DVT), is a common complication after trauma with rates as high as 28% despite thromboprophylaxis.[1–3] Recent data from our institution demonstrate a 10% incidence of VTE despite protocolized thromboprophylaxis and duplex venous surveillance.[4,5] Current VTE prediction models lack accuracy and do not objectively account for markers of hypercoagulability.[6] Thus, VTE in trauma continues to be unpredictable and occurs in patients perceived to be at low risk.

Objective assessment of hypercoagulability may improve prediction. Traditional plasma-based coagulation tests, such as prothrombin time, partial thromboplastin time, and international normalized ratio, are objective yet not predictive of VTE, because they fail to completely evaluate the clotting process.[7] Thromboelastography (TEG), on the other hand, provides a comprehensive evaluation of the viscoelastic properties of whole blood from initial clot formation through fibrinolysis, and may be predictive of VTE.

Previous studies investigating the use of TEG in predicting risk of symptomatic VTE have yielded conflicting results and did not include duplex venous surveillance in study protocols.[8–10] Surveillance will detect asymptomatic DVT, which are far more common than symptomatic DVT.[1,11]

We undertook a prospective study of TEG to evaluate its utility in predicting symptomatic and asymptomatic VTE. We hypothesized that the VTE rate is higher in trauma patients with hypercoagulability identified by TEG than those without a hypercoagulable TEG.

PATIENTS AND METHODS

After approval by the Scripps Institutional Review Board, we conducted a prospective cohort study on adult trauma patients admitted from August 1, 2013, to November 30, 2015, as part of the Consortium of Leaders in the Study of Traumatic Thromboembolism (CLOTT). All adult patients admitted to our urban, Level I trauma center with hospital length of stay of 48 hours or longer during the study period were eligible. Only direct admissions were included, and patients transferred hospital-to-hospital were excluded. A kaolin TEG sample was drawn immediately on patient arrival to the trauma bay with initial laboratory studies. Samples were citrated then recalcified in the laboratory according to manufacturer's guidelines, and all samples were run within 2 hours of the draw time. The TEG samples were run at 37°C on one of two available TEG 5000 machines (Haemonetics Corporation, Braintree, MA) by two certified laboratory technologists in the hospital laboratory. The TEG 5000 machines underwent quality control assessment every eight hours, and samples not meeting reporting standards were re-run, if possible, or not reported. The TEG parameters of reaction time (R), coagulation time (K), alpha angle (α), maximum amplitude (MA), clot strength (G), and percent clot lysis at 30 minutes (LY30) were recorded for each sample.

Individual TEG parameters were first examined separately in univariate analysis as continuous variables. Each parameter was also examined as a categorical variable, with a hypercoagulable parameter defined as a value above or below, as appropriate, the limit of the reference range for our healthcare system. "Hypercoagulable TEG," examined as a collection of the individual parameters, was defined *a priori* as R below 5 minutes, α above 72 degrees, and/or MA above 74 mm, which represent the cut-offs of reference ranges. These values were chosen as they represent three important contributors to clot formation (cascade activation, fibrin cross-linking, and clot strength) while eliminating calculated values (such as G) and values that do not include a hypercoagulable range (such as LY30).

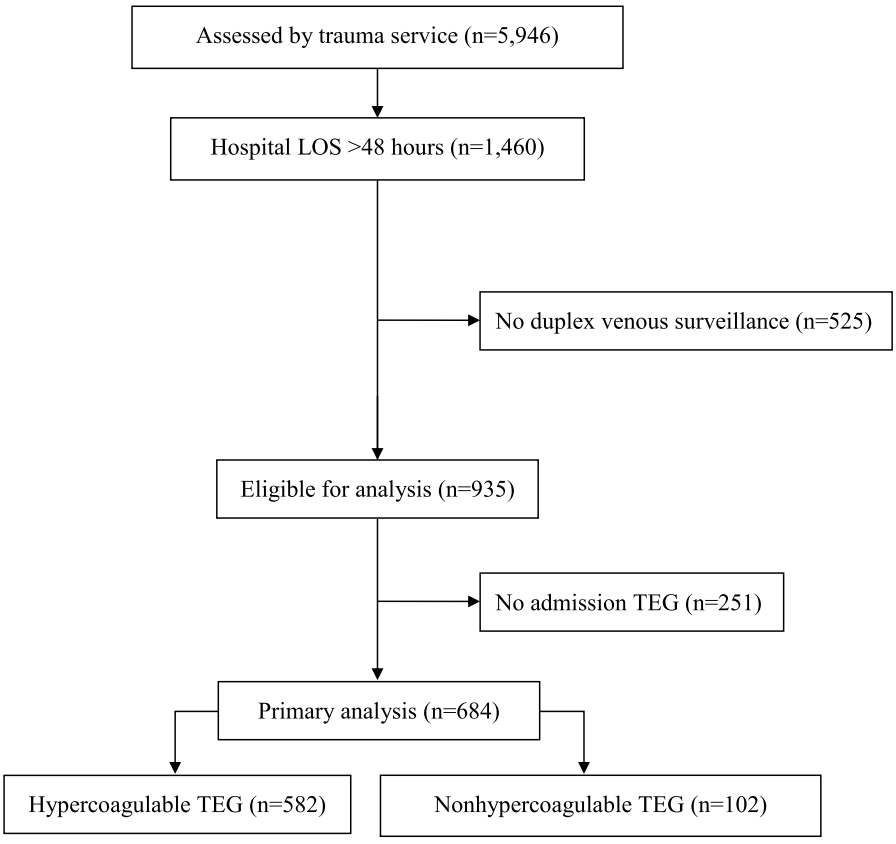
Data for 45 VTE risk factors were also collected concurrently. These risk factors were chosen based on previously reported risk factors and work from the CLOTT study.[12–20] All patients received mechanical and/or pharmacologic prophylaxis. Mechanical prophylaxis consisted of knee-length sequential compression devices except where injuries prohibited such placement,

in which case foot pumps were used as applicable. Standard pharmacologic prophylaxis during the study period was 5,000 units of unfractionated heparin injected subcutaneously every 8 hours, except when low-molecular weight heparin was expressly requested by a consulting service. The compliance rate for mechanical prophylaxis was 94% during the study, with 83% of patients on chemoprophylaxis receiving unfractionated heparin.

Patients were monitored for VTE events including asymptomatic and symptomatic DVT (brachial/axillary/subclavian in upper extremity, calf veins/popliteal/femoral/iliac in lower extremity, internal jugular, inferior vena cava, mesenteric, portal, and splenic) or PE. DVT was defined as thrombosis in a nonsuperficial vein detected by duplex venous surveillance using the standard criteria.[4,21] Patients were actively followed for DVT with our surveillance protocol. This protocol included lower-extremity duplex ultrasounds twice weekly for all patients in the intensive care unit and once weekly for all other patients until discharge. Duplex ultrasounds were performed from groin to ankle by one of two vascular technologists, who remained on staff throughout the study period. Studies were read by a board-certified radiologist blinded to the patients' study status and TEG results. Diagnostic venous duplex ultrasound and computed tomography-pulmonary angiography were performed to evaluate patients suspected of having symptomatic DVT or PE, respectively. Signs and symptoms prompting diagnostic venous duplex imaging, per protocol, included a change in previous extremity examinations in any of the following: erythema, warmth, pain, edema, or tenderness. Signs and symptoms prompting computed tomography-pulmonary angiography, per protocol, included sudden onset or worsening dyspnea, tachypnea, tachycardia (>100 beats per minute), chest pain, hemoptysis, decrease in oxygen saturation to less than 92% or a drop of 5% from baseline, new hypoxemia (arterial partial pressure of oxygen < 80 mm of mercury), new hypocapnia (arterial partial pressure of carbon dioxide < 40 mm of mercury), or evidence of right heart strain on electrocardiogram or echocardiogram. These studies were also interpreted by a staff radiologist blinded to study status and TEG results.

The primary analysis was performed only on patients with at least one duplex venous surveillance to reduce the effect of surveillance bias. The primary exposure was hypercoagulability on TEG as defined above. The primary outcome was lower-extremity DVT.

Data were managed and analyzed using Stata/MP version 11.2 (StataCorp LP, College Station, TX). Categorical variables were compared using χ^2 tests. Continuous variables were compared using Student's *t* tests. Nonparametric tests were used to compare non-normally distributed variables. After bivariate analysis of clinical and demographic variables available at time of admission, variables of interest with *p* values of 0.100 or less were included in multivariate analysis. Multiple logistic regression



LOS, length of stay; TEG, thromboelastography

Figure 1. Patient selection diagram.

TABLE 1. Patient Characteristics

Characteristics	Hypercoagulable TEG (n = 582)	Non-Hypercoagulable TEG (n = 102)	Total (n = 684)	*p*
Male, n (%)	397 (69)	88 (87)	485 (71)	<0.0001
GCS score, median (IQR)	15 (14–15)	15 (14–15)	15 (14–15)	0.73
Age, mean (SD), y	50.0 (22.2)	46.7 (23.1)	49.5 (22.3)	0.17
ISS, median (IQR)	14 (9–22)	10 (9–17)	13 (9–21)	0.05
Head AIS score, median (IQR)	2 (0–4)	2 (0–3)	0 (0–4)	0.94
Chest AIS score, median (IQR)	0 (0–2)	0 (0–0)	0 (0–2)	0.1
Extremity AIS score, median (IQR)	1 (0–2)	0 (0–2)	1 (0–2)	0.65
Hospital LOS, mean (SD), d	9.1 (11.1)	7.6 (8.2)	8.9 (10.7)	0.28
ICU LOS, mean (SD), d	3.2 (6.2)	2.7 (5.4)	3.1 (6.1)	0.31
Ventilator days, mean (SD)	1.9 (5.3)	1.1 (3.6)	1.8 (5.1)	0.1
In-hospital death, n (%)	26 (5)	3 (3)	29 (4)	0.6

GCS, Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation; ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; LOS, length of stay; ICU, intensive care unit.

was used to evaluate the relationship between VTE risk factors and identify outcomes, adjusting for all relevant covariates. Statistical significance was attributed to p less than 0.050.

RESULTS

During the study period, 5,946 patients were evaluated by the trauma service, including 1,160 emergency department consultations and 4,786 trauma admissions. Of these, 1,460 had a hospital length of stay greater than 48 hours. A total of 983 new trauma patients were evaluated with TEG on admission. Of the 983 patients with TEG results, 684 (69.6%) received at least one surveillance ultrasound during the index admission and were included in the primary analysis (Fig. 1). Hypercoagulability based on admission TEG was seen in 582 (85.1%) of the 684 patients. Demographics were similar between those patients who were hypercoagulable and those who were not except for sex—there was a significantly higher percentage of males in the hypercoagulable group (Table 1).

Lower-extremity DVT was found on duplex venous surveillance in 99 (14.5%) patients. Two PEs associated with lower-extremity DVT were diagnosed by computed tomography-pulmonary angiography. Three upper-extremity DVTs associated with lower-extremity DVT were also diagnosed and confirmed on diagnostic ultrasound. The rate of lower-extremity DVT was significantly higher in patients with hypercoagulable TEG than in those without hypercoagulable TEG (15.6% vs. 8%; $p = 0.039$). No single TEG parameter was significantly associated with DVT (Table 2).

Bivariate analysis revealed a number of factors associated with DVT (Table 3). From this analysis, variables with $p \leq 0.100$ were included in the final logistic regression analysis. This showed that hypercoagulable TEG remained significantly associated with DVT after adjustment for relevant covariates available at time of admission (traumatic brain injury, sex, age, international normalized ratio, stable spine fracture, unstable spine fracture, pelvic fracture, venous injury, blood product transfusion), with an odds ratio of 2.41 (95% confidence interval, 1.11–5.24; $p = 0.026$) (Table 4). When other covariates not available at time of admission were included (mechanical ventilation days, Injury Severity Score, active in-hospital infection, pharmacological prophylaxis, ambulation status, hospital length of stay), hypercoagulable TEG lost statistical significance ($p = 0.060$). Considered alone, hypercoagulable TEG predicted DVT with a high sensitivity (91.9%) but with a very low specificity (16.1%). Consequently, hypercoagulable TEG had a very low positive predictive value (15.6%) and a very high negative predictive value (92.2%), with an area under the receiver operating characteristic curve of 0.54.

DISCUSSION

We sought to evaluate TEG as a marker of hypercoagulability to establish its utility as a risk factor for VTE. This prospective study showed in both univariate and multivariate analyses that hypercoagulable TEG was associated with a significantly higher rate of lower-extremity DVT. Although none of the individual TEG parameters were significantly associated with DVT, the combination of R, α, and MA was a useful risk factor available at time of admission. We were able to accept our hypothesis that the VTE rate is higher in trauma patients with hypercoagulability identified by TEG than in those without hypercoagulable TEG.

VTE has traditionally been attributed to venous stasis, endothelial injury, and hypercoagulability, as identified by

TABLE 2. TEG Variables in Patients With and Without DVT

TEG Variables	DVT (n = 99)	No DVT (n = 585)	*p*
R, mean (SD), min	4.3 (1.6)	4.1 (1.2)	0.23
α, mean (SD), degrees	71.3 (4.4)	71.0 (5.7)	0.57
MA, mean (SD), mm	65.2 (5.9)	65.0 (6.6)	0.85
G, mean (SD), dynes/cm^2	9.8 (2.5)	9.9 (3.8)	0.72
LY30, mean (SD), %	2.1 (5.9)	1.8 (5.0)	0.52
R < 5 min, n (%)	82 (83)	451 (77)	0.20
MA > 74 mm, n (%)	19 (19)	122 (21)	0.71
α > 72°, n (%)	49 (49)	280 (48)	0.76
G > 11 dynes/cm^2, n (%)	26 (26)	157 (27)	0.91
No. hypercoagulable parameters, mean (SD)	1.5 (0.8)	1.5 (0.9)	0.57

TABLE 3. Bivariate Associations of Risk Factors With DVT

Risk Factors	DVT (n = 99)	No DVT (n = 585)	*p*
Active infection after admission, n (%)	26 (26)	73 (12)	<0.0001
Admission vitals: temperature, mean (SD)	36.7 (0.54)	36.6 (0.53)	0.11
C reactive protein, mean (SD)	26.7 (48)	18.4 (38)	0.13
Traumatic brain injury, n (%)	41 (41)	192 (33)	0.1
Spinal cord injury, n (%)	2 (2)	5 (1)	0.27
Operation time ≥2 h, n (%)	16 (16)	73 (12)	0.31
Unstable spinal fracture, n (%)	10 (10)	29 (5)	0.04
Stable spinal fracture, n (%)	14 (14)	74 (13)	0.68
Ambulation during hospital stay, n (%)	19 (19)	241 (41)	<0.0001
Lower-extremity amputation, n (%)	2 (2)	0 (0)	0.02
Lower-extremity long bone fracture, n (%)	25 (25)	143 (24)	0.86
Pelvic fracture, n (%)	15 (15)	46 (8)	0.02
Foot fracture with bed rest >72 h, n (%)	10 (10)	63 (11)	0.84
Femoral central venous catheter placement, n (%)	2 (2)	8 (1)	0.64
Inferior vena cava filter placement, n (%)	25 (25)	20 (3)	<0.0001
Named vein injury, n (%)	3 (3)	3 (0.5)	0.04
Packed red blood cell transfusion, n (%)	32 (32)	82 (14)	<0.0001
Platelet transfusion, n (%)	16 (16)	42 (7)	0.003
Fresh frozen plasma transfusion, n (%)	21 (21)	56 (10)	0.001
Admission vitals: systolic blood pressure, mean (SD)	130 (29)	134 (29)	0.18
Received mechanical prophylaxis, n (%)	95 (96)	534 (91)	0.16
Received chemoprophylaxis, n (%)	68 (69)	332 (57)	0.03
Missed/interrupted chemoprophylaxis, n (%)	31 (46)	113 (34)	0.07
Received tranexamic acid, n (%)	1 (1)	2 (0.3)	0.38
Received cryoprecipitate, n (%)	0 (0)	1 (0.2)	1
Prothrombin complex concentrate, n (%)	0 (0)	6 (1)	0.6
Male, n (%)	78 (79)	407 (70)	0.08
GCS, median (IQR)	15 (13–15)	15 (14–15)	0.26
Age, mean (SD), y	55.6 (20.4)	48.4 (22.5)	0.003
ISS, median (IQR)	17 (10–25)	12 (9–19)	0.002
Head AIS, median (IQR)	2 (0–3)	2 (0–4)	0.46
Chest AIS, median (IQR)	0 (0–3)	0 (0–2)	0.04
Extremity AIS, median (IQR)	2 (0–3)	0 (0–2)	0.0002
Hospital LOS, mean (SD), d	15.4 (14.1)	7.8 (9.6)	<0.0001
ICU LOS, mean (SD), d	7.5 (11.1)	2.4 (4.3)	<0.0001
Mechanical ventilation, mean (SD), d	5.2 (9.8)	1.2 (3.5)	<0.0001
In-hospital death, n (%)	7 (7)	22 (4)	0.14
Received blood products, n (%)	35 (35)	117 (20)	0.001

Virchow.[22] Using this construct, numerous prediction models have been created and validated. The two most common VTE models used in trauma, the Risk Assessment Profile,[23] and the Trauma Embolic Scoring System,[14] were developed based on consensus opinion of risk factors and do not directly assess hypercoagulability. Despite identification of groups at higher and lower risk, these models lack accuracy in predicting VTE. Most patients at "high risk" will not be diagnosed with a DVT, and patients at "low risk" still develop DVT and occasionally fatal PE, albeit at a lower incidence.[15] In one validation study,[6] this combination produced a receiver operating characteristic curve of only 0.66 for both models. Obviously, further identification of risk factors is needed, preferably isolating those available on admission so that a clinician can appropriately guide prophylaxis and surveillance as early as possible.

TEG has been used to evaluate coagulation status for over 50 years, and it reliably identifies the presence of a hypercoagulable state after traumatic injury.[9,24–26] Using TEG exclusively to predict thrombotic complications has been studied previously. Park et al.[26] found that TEG could not distinguish between patients who developed VTE and those who did not. In contrast, three previous studies have demonstrated TEG to be predictive of thrombotic complications.[8–10] These studies each have significant limitations. All three were completed at facilities without a DVT surveillance program. Since a majority of DVTs diagnosed after trauma are asymptomatic, most VTE events were likely unaccounted.[27] Additionally, the predictive TEG parameters were not consistent among the studies. Thus, uncertainty exists regarding the ability to predict VTE events based on TEG. The present study was designed to address that specific knowledge gap.

Our surveillance protocol is a rigorous approach to diagnosing lower-extremity DVT. This standardized step is essential in calculating the true incidence of in-hospital lower-extremity DVT while minimizing surveillance bias.[27] The 45 other VTE risk factors analyzed in our study represent an inclusive set of all established variables known to date, strengthening the statistical analysis and transmissible message. At the same time, several limitations exist in the study. TEG samples were drawn immediately upon patient arrival, but the time lapse between the injury and the patient's arrival is unknown. As the coagulation profile changes over time after injury,[28] this limitation introduces uncertainty into the analysis that cannot be reliably corrected by prehospital data. A systematic bias, therefore, is a possibility if patients who arrived to the trauma bay more quickly were not equally distributed. This potential bias is limited by our rapid emergency medical system response times and transport times in our urban catchment area, with a mean scene-to-hospital time of 8.8 minutes to 13.7 minutes, depending on city region.[29] Additionally, we found that patients were often discharged before their first screening duplex ultrasound, a number totaling 30% of the target population.

The vast majority (85.1%) of trauma patients requiring admission to our institution were hypercoagulable, which led to a low positive predictive value. At the same time, the prevalence of hypercoagulability prompts the trauma surgeon to examine TEG results carefully regardless of the perceived VTE risk level

TABLE 4. Multivariate Analysis of TEG and Other Admission Risk Factors for DVT

Risk Factors	OR	95% CI	*p*
Hypercoagulable TEG	2.41	1.11–5.24	0.026
Traumatic brain injury	1.49	0.94–2.35	0.088
Female sex	0.37	0.21–0.66	0.001
Unstable spine fracture	2.18	0.96–4.93	0.062
Pelvic fracture	2.17	1.09–4.33	0.028
Venous injury	4.89	0.81–29.34	0.083
Transfusion	1.90	1.16–3.12	0.011
Age, y	1.02	1.01–1.03	<0.001

OR, odds ratio; CI, confidence interval.

for a given patient. As the objective of the study was to identify TEG as a risk factor for DVT, rather than a definitive predictor of DVT, the area under the receiver operating characteristic curve of 0.54 is reasonable. This figure should be compared to the areas under the receiver operating characteristic curve for the Risk Assessment Profile and Trauma Embolic Scoring System, both 0.66 in a recent study, which are billed as complete models rather than examinations of a single risk factor.[6]

This high prevalence of hypercoagulability conflicts with several previous reports of coagulopathy as evaluated by TEG.[7,24–26,30–35] One potential explanation lies in our categorization of hypercoagulable versus non-hypercoagulable TEG. Any of the three variables of interest pushed a patient into the hypercoagulable category. Also, many TEG studies focus on "major trauma admissions,"[25,31–33,35] whereas we included all new trauma admissions. As the burden of injury decreases, it is likely that fewer of these patients are coagulopathic. Regarding an additional limitation, hypercoagulable TEG did not remain statistically significant as an independent predictor when risk factors available after admission were included in the analysis. However, as clinically useful prediction models must rely on exposure variables available before the adverse event, we view the multivariate analysis including only the admission variables as more relevant to the practicing surgeon. Finally, as a single center study, external validation for this work remains an area for future research.

Trauma patients remain at an elevated risk of developing DVT even after adjustment for relevant clinical factors which are encompassed in the current VTE prediction models. TEG is an objective test, which is available on admission and provides insight into the coagulability status of the patient. Trauma patients are at high risk for VTE. The rate of DVT doubles in patients with hypercoagulable TEG indices, despite prophylaxis regimens. This association established TEG as a useful metric for assessing DVT risk. This finding may be particularly relevant in patients otherwise perceived to be at low risk.

AUTHORSHIP

J.B.B., J.B., A.L.Z., and S.R.S. designed this study. J.B.B., J.B., A.L.Z., J.D.W., and P.R.L. collected and analyzed the data. J.B.B., J.B., A.L.Z., J.D.W., P.R.L., M.J.S., V.B., and S.R.S. participated in data interpretation and manuscript preparation. All authors approved the final version of the manuscript.

DISCLOSURE

Conflicts of Interest: There are no relevant financial relationships or any sources of support in the form of grants, equipment, or drugs. However, co-author Vishal Bansal, MD, is currently Chief Scientific Officer and co-founder of Oxeia Biopharmaceuticals, Inc. which focuses on drug treatments for concussion. Martin Schreiber was Haemoscope Consultant. For the remaining co-authors, no conflicts, actual or potential, are declared.
Source of Funding: None.

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