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ORIGINAL ARTICLE

Functional Coagulation Differences Between Lobar and Deep Intracerebral Hemorrhage Detected by Rotational Thromboelastometry: A Pilot Study

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Abstract

Background: Lobar intracerebral hemorrhage (ICH) is known to have better clinical outcomes and preliminary evidence of less hematoma expansion compared to deep ICH. No functional coagulation differences between lobar and deep ICH have been identified using traditional plasma-based coagulation tests. We investigated for coagulation differences between lobar and deep ICH using whole-blood coagulation testing (Rotational Thromboelastometry: [ROTEM]).

Methods: Clinical, radiographic, and laboratory data were prospectively collected for primary ICH patients enrolled in a single-center ICH study. Patients with preceding anticoagulant use or admission coagulopathy on traditional laboratory testing were excluded. Lobar and deep ICH patients receiving admission ROTEM were analyzed. Linear regression was used to assess the association of ICH location with coagulation test results after adjusting for potential confounders.

Results: There were 12 lobar and 19 deep ICH patients meeting inclusion criteria. Lobar ICH patients were significantly older and predominantly female. Lobar ICH had faster intrinsic pathway coagulation times (139.8 vs 203.2 s; 95% CI −179.91 to −45.96; $p=0.002$) on ROTEM testing compared to deep ICH after adjusting for age, sex, and hematoma volume. This revealed functional coagulation differences, specifically quicker clot formation in lobar compared to deep ICH. No differences were noted using traditional coagulation testing (prothrombin time/partial thromboplastin time/platelet count).

Conclusions: Our pilot data may suggest that there are functional coagulation differences between lobar and deep ICH identified using ROTEM. Whole-blood coagulation testing may be useful in assessing coagulopathy in ICH patients and in determining reversal treatment paradigms, though further work is needed.

Keywords: Intracerebral hemorrhage, Location, Lobar, Deep, Coagulopathy, Rotational thromboelastometry

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Introduction

The majority of intracerebral hemorrhages (ICH) are either lobar or deep in location. Despite larger baseline hematoma volumes [1], lobar ICH is known to have better outcome [2] and possibly less hematoma expansion (HE) [3] compared to deep ICH suggesting different mechanisms of injury between locations. However, current ICH treatment paradigms do not account for ICH location in coagulopathy treatment strategies as there have not been identifiable differences in functional coagulation using plasma-based coagulation testing between these locations [2–4]. Though helpful in detecting coagulopathy in patients taking anticoagulant medications, these plasma-based tests (prothrombin time [PT] and partial thromboplastin time [PTT]) are limited in identifying coagulopathy in non-anticoagulated patients and identifying those at risk of HE as they were not originally designed to predict coagulopathy in active bleeding [5, 6].

Whole-blood viscoelastic hemostatic assays, Rotational Thromboelastometry (ROTEM) and Thromboelastography (TEG), are separate functional coagulation testing modalities that evaluate all components required for hemostasis (platelets, fibrinogen, coagulation factors, erythrocytes) and their interactions rather than each component separately. These tests use a cell-based model of coagulation to assess coagulation times in addition to clot strength and lysis, rather than just the in vitro time to initial fibrin formation provided by plasma-based tests.

Prior studies using viscoelastic whole-blood assessment of functional coagulation (using TEG) identified associations of slower clot formation with ICH patients that go on to develop HE [7] in addition to those with worse outcomes not seen with traditional plasma-based tests [8]. However, these results did not assess for coagulation differences stratified by location. We hypothesized that ROTEM would identify faster clot formation in lobar compared to deep ICH patients.

Methods

Spontaneous ICH patients admitted to Columbia University Irving Medical Center were enrolled in a prospective, Institutional Review Board-approved ICH cohort study: ICH Outcomes Project. Baseline clinical characteristics, neuroimaging features, laboratory results (including ROTEM), and interventions were recorded. Informed consent was obtained by patients or family when appropriate.

ROTEM

ROTEM (Instrumentation Laboratory, MA) is an FDA-approved viscoelastic assessment of functional coagulation using whole blood. Consequently, ROTEM is able to assess all three stages of hemostasis: (1) clot formation via coagulation time, (2) clot strength via maximum clot firmness (MCF), and (3) clot stability/lysis via maximum lysis (ML) (Fig. 1a). It is worth noting that while ROTEM provides similar functional coagulation kinetics and properties to TEG, there are differences in operating characteristics and testing assays compared to TEG. Specifically, ROTEM utilizes rotation impedance with a rotating pin, whereas TEG utilizes pin transduction with a fixed position pin to detect clotting kinetics and strength. In addition, ROTEM provides separate evaluation for fibrinogen contribution to clot formation (FIBTEM; cytochalasin-D blocking platelet contribution) as well as separate assessments of the extrinsic (EXTEM; tissue factor activation) and intrinsic (INTEM; contact activation) coagulation pathways.

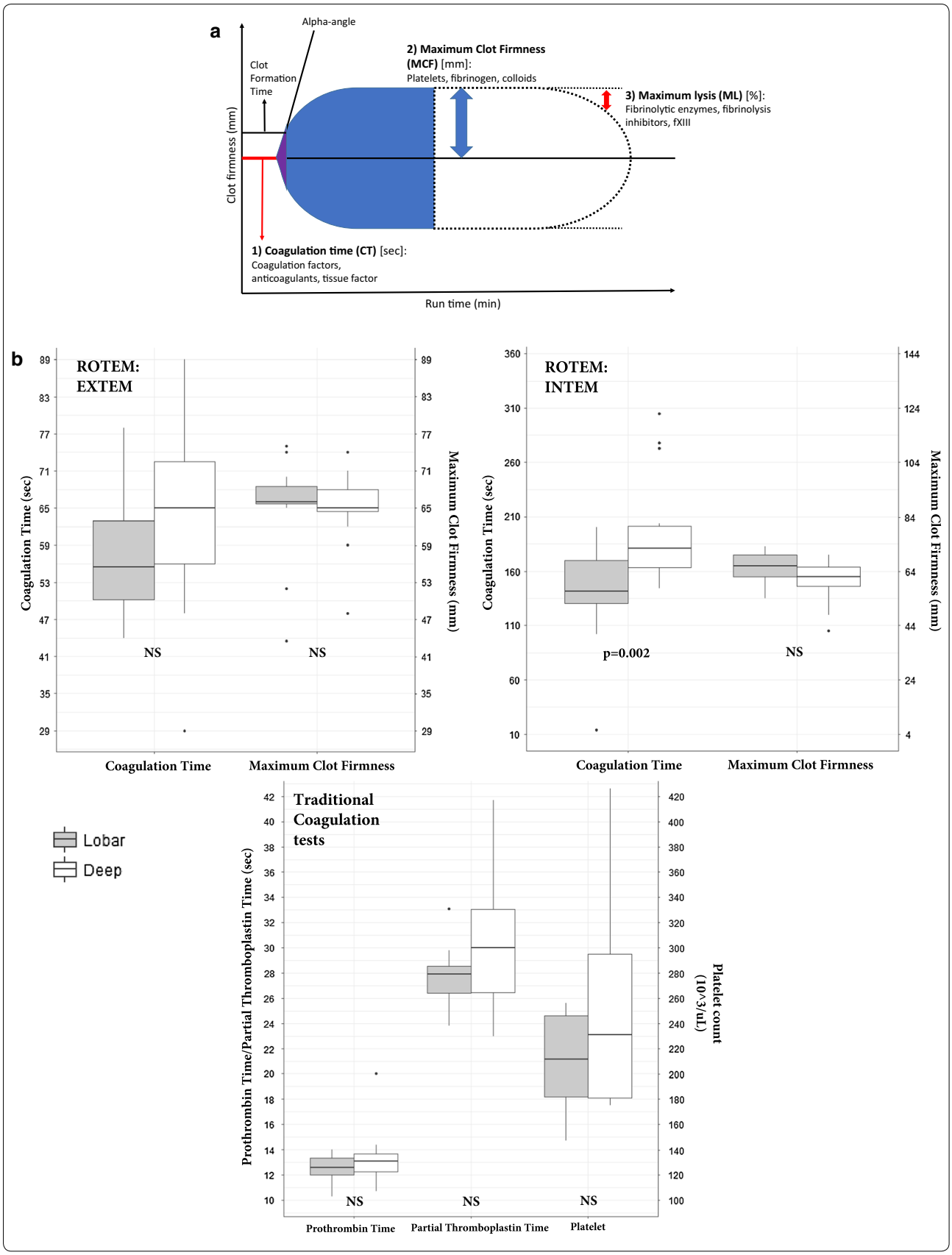
The ROTEM in this study was located in the intensive care unit and was utilized as a point of care device. Testing was performed by trained practitioners creating a cohort sample of convenience based on expert personnel availability. ROTEM samples were obtained from three milliliters of discarded whole blood drawn clinically for traditional admission coagulation testing. Samples were collected into a citrated tube and run within 60 min of collection. Times from symptom onset to ROTEM were recorded. Primary ROTEM outcomes were coagulation time, MCF, ML among EXTEM and INTEM assays and MCF in FIBTEM assay. Weekly quality control (normal/abnormal) tests and daily calibration, verification, and operational checks were run to ensure validity.

Patient Selection

Primary lobar or deep ICH patients receiving admission ROTEM (prior to hemorrhage reversal treatment) between 2013 and 2017 were included for analysis for this pilot study. ICH located at the cortical/subcortical junction was adjudicated as lobar, and ICH in the thalamus/basal ganglia as deep, through weekly consensus meetings of study physicians. Mixed lobar and deep ICH, brainstem/infratentorial ICH, secondary ICH (vascular malformation, aneurysm, malignancy, ischemic stroke with hemorrhagic transformation), traumatic ICH,

(See figure on next page)

Fig. 1 **a** ROTEM parameters. **b** Functional coagulation differences between lobar and deep ICH. **c** ROTEM differences between lobar and deep ICH (results from single patient from each ICH location). *ROTEM* rotational thromboelastometry, *ICH* intracerebral hemorrhage, *EXTEM* extrinsic pathway, *INTEM* intrinsic pathway, *MCF* maximum clot firmness, *NS* nonsignificant. ROTEM reference ranges: EXTEM coagulation time 43–82 s; EXTEM MCF 52–70 mm; INTEM coagulation time 122–208 s; INTEM MCF 51–72 mm; FIBTEM MCF 7–24 mm


a
Alpha-angle
Clot Formation Time
2) Maximum Clot Firmness (MCF) [mm]:
Platelets, fibrinogen, colloids
3) Maximum lysis (ML) [%]:
Fibrinolytic enzymes, fibrinolysis inhibitors, fXIII
Clot firmness (mm)
1) Coagulation time (CT) [sec]:
Coagulation factors, anticoagulants, tissue factor
Run time (min)
b
ROTEM: EXTEM
Coagulation Time (sec)
Maximum Clot Firmness (mm)
NS
NS
Coagulation Time
Maximum Clot Firmness
ROTEM: INTEM
Coagulation Time (sec)
Maximum Clot Firmness (mm)
p=0.002
NS
Coagulation Time
Maximum Clot Firmness
Lobar
Deep
Traditional Coagulation tests
Prothrombin Time/Partial Thromboplastin Time (sec)
Platelet count (10^3/uL)
NS
NS
NS
Prothrombin Time
Partial Thromboplastin Time
Platelet

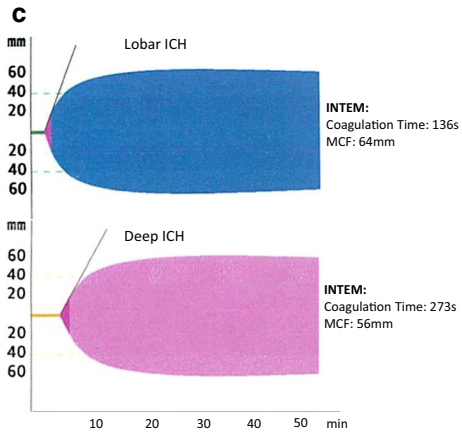


Fig. 1 continued

patients with preceding anticoagulant use, or patients with evidence of admission coagulopathy using SMASH-U criteria (International normalized ratio [INR] > 2.0, platelet count < 50×10^3/uL) [9] or plasma testing thresholds of PT > 20 s and PTT > 50 s were excluded (eFigure 1). Patients were managed according to American Heart Association guidelines [10] with further management protocol details described previously [11].

Statistical Analysis

Analyses were performed using SPSS (ver23). Intergroup differences (lobar vs deep) were determined applying Mann–Whitney *U* or *t* test for continuous variables and χ^2 for categorical variables. Normality was met with continuous ROTEM outcome variables, and multivariable linear regression was performed to assess association of ICH location (lobar vs deep) as the primary independent predictor variable with ROTEM results as the primary outcome dependent variable after adjusting for previously identified covariates of coagulopathy: age and sex [12]. Baseline hematoma volume was also entered into the primary model a priori given expected baseline differences between lobar and deep locations resulting in tissue injury differences that would affect functional coagulation differences. Coagulation tests were chosen as the dependent outcome variable in these models as we hypothesized that differing regions of ICH location would result in different injury patterns resulting in subsequent coagulation differences. Separate models were performed with each primary ROTEM outcome and plasma coagulation tests. Other significant intergroup differences thought to potentially affect coagulation were added to the model in additional sensitivity analyses. Statistical significance was evaluated at $p < 0.05$.

Results

Of 146 eligible patients, 55 received ROTEM and 31 were ultimately included for analysis. While the prevalence of lobar ICH was higher in our inclusion cohort compared to those excluded, other baseline characteristics and traditional coagulation tests were comparable. Inclusion and exclusion details are further described in eFigure 1. Of these 31 primary ICH patients with admission ROTEM, 12 were lobar (39%) and 19 were deep (61%). The overall cohort was racially diverse (26% white). Intergroup comparisons are shown in Table 1. Lobar ICH patients were significantly older and predominantly female. There were no significant differences in baseline clinical/imaging characteristics (including baseline hematoma volume) or time to ROTEM/neuroimaging. There were no significant differences in systolic blood pressure; however, there was significantly lower diastolic blood pressure in lobar (93 vs 118 mmHg; $p = 0.01$) compared to deep ICH.

There were no significant differences in traditional coagulation tests (PT/PTT/INR/platelet) between groups. However, there were significantly faster ROTEM INTEM coagulation times in lobar compared to deep ICH (mean 139.8 vs 203.2 s). No other significant intergroup ROTEM differences were observed (Table 2).

Multivariable linear regression revealed an association of lobar ICH with faster INTEM coagulation times (*B*-coeff: −112.94; 95% CI −179.91 to −45.96; $p = 0.002$) compared to deep ICH after adjusting for age, sex, and baseline hematoma volume (Table 2). Sensitivity models adjusting for race, blood pressure, or time to ROTEM acquisition did not change the result. There was no association of lobar ICH location and the analogous plasma-based test for INTEM coagulation time, the PTT (*B*-coeff: −3.85; 95% CI −9.17 to 1.47; $p = 0.15$) after adjusting for the same covariates (Fig. 1b, c).

Table 1 Lobar versus deep ICH characteristics

	All ICH *N* = 31	Lobar ICH *N* = 12	Deep ICH *N* = 19	*p* value
Age: mean (SD)	63 (16)	75 (15)	56 (11)	<0.001
Female: *N* (%)	14 (45)	9 (75)	5 (26)	0.01
Race: *N* (%)				
White	8 (26)	5 (42)	3 (16)	0.33
Black	9 (29)	2 (17)	7 (37)	
Hispanic	6 (19)	3 (25)	3 (16)	
Other	8 (25)	2 (17)	6 (32)	
Medical history: *N* (%)				
Dyslipidemia	5 (16)	4 (33)	1 (5)	0.06
Hypertension	22 (71)	8 (67)	14 (74)	0.65
Diabetes	3 (10)	1 (8)	2 (11)	1.00
Atrial fibrillation	1 (3)	1 (8)	0 (0)	0.39
Prior antiplatelet use: *N* (%)	6 (19)	3 (25)	3 (16)	0.66
Clinical/radiographic				
Admit SBP: mean (SD)	183 (44)	176 (30)	188 (56)	0.52
Admit DBP: mean (SD)	107 (24)	93 (24)	118 (23)	0.01
ICH score: median (IQR)	2 (1–3)	3 (1–4)	2 (1–3)	0.42
ICH volume (mL): median (IQR)	25 (8–46)	46 (16–52)	20 (7–36)	0.27
IVH: *N* (%)	16 (52)	4 (33)	12 (63)	0.26
Symptom onset to ROTEM (h): median (IQR)	11 (3.7–17)	13.6 (7.1–23.6)	9.8 (3.2–16.8)	0.24
Traditional coagulation laboratory testing: mean (SD)				
Prothrombin time (s)	12.9 (1.7)	12.6 (1.1)	13.3 (2.1)	0.29
Partial thromboplastin time (s)	28.5 (4.1)	27.2 (2.7)	29.6 (4.8)	0.16
Platelet count (10^3/uL)	240 (68)	210 (40)	246 (72)	0.15

CI confidence interval, *DBP* diastolic blood pressure, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *IVH* intraventricular hemorrhage, *ROTEM* rotational thromboelastometry, *SBP* systolic blood pressure, *SD* standard deviation

Table 2 Univariable and multivariable linear regression assessing association of lobar ICH location with ROTEM results

Outcome	All ICH *N* = 31 Mean (SD)	Lobar ICH *N* = 12 Mean (SD)	Deep ICH *N* = 19 Mean (SD)	Unadjusted-*B* (95% CI)	*p* value	Adjusted-*B** (95% CI)	*p* value
EXTEM CT (s)	62.4 (14.4)	57.4 (10.7)	65.5 (15.7)	−8.06 (−18.66 to 2.54)	0.13	−2.25 (−18.43 to 13.93)	0.78
EXTEM MCF (mm)	65.0 (3.7)	64.8 (8.8)	65.2 (5.4)	−0.42 (−5.62 to 4.78)	0.87	−1.39 (−9.26 to 6.48)	0.72
EXTEM ML (%)	8.8 (5.7)	8.3 (6.4)	9.2 (5.4)	−0.91 (−5.29 to 3.47)	0.68	−1.48 (−8.53 to 5.57)	0.67
INTEM CT (s)	178.7 (67.1)	139.8 (48.1)	203.2 (66.7)	−63.42 (−108.89 to −17.94)	0.01	−112.94 (−179.91 to −45.96)	0.002
INTEM MCF (mm)	62.3 (6.8)	65.5 (5.7)	60.5 (6.9)	4.93 (−0.10 to 9.96)	0.06	7.58 (−0.53 to 15.69)	0.07
INTEM ML (%)	8.5 (5.5)	8.3 (5.8)	8.6 (5.4)	−0.29 (−4.49 to 3.89)	0.89	−0.76 (−7.45 to 5.94)	0.82
FIBTEM MCF (mm)	23.4 (9.9)	24.5 (8.0)	22.6 (11.1)	1.87 (−5.71 to 9.44)	0.62	−0.04 (−11.91 to 11.83)	0.99

CI confidence interval, *CT* coagulation time, *EXTEM* extrinsic pathway, *FIBTEM* fibrinogen assay, *ICH* intracerebral hemorrhage, *INTEM* intrinsic pathway, *MCF* maximal clot firmness, *ML* maximum lysis, *ROTEM* rotational thromboelastometry, *SD* standard deviation

*Adjusted for age, sex, baseline hematoma size

Discussion

In a cohort of primary ICH patients without preceding anticoagulation use or admission laboratory coagulopathy, we identified functional coagulation differences between lobar and deep ICH using ROTEM. We identified faster intrinsic pathway activation in lobar compared to deep ICH on ROTEM not observed with the analogous plasma-based coagulation test PTT. Our cohort's lobar ICH patients were older and more likely female than our deep ICH patients, which are known factors for hypercoagulability. However, lobar ICH continued to be associated with faster INTEM coagulation times after adjusting

for these differences in addition to baseline hematoma size suggesting faster intrinsic coagulation factor activation of thrombin to initiate clot formation in lobar ICH. The presence of larger amplitude INTEM MCF in lobar ICH, though suggestive of stronger clot formation and more optimal hemostasis, was clinically small and not statistically significant ($p = 0.07$) in comparison with the large INTEM coagulation time differences. No differences were observed in fibrinolysis/clot stability (ML).

These pilot findings are hypothesis generating at this point but may suggest differences in functional coagulation and more optimal hemostasis in lobar compared to deep ICH. This appeared to be driven by faster and potentially stronger clot formation rather than differences in clot breakdown/lysis in our ICH cohort. The pathophysiologic mechanism behind more rapid activation of the intrinsic rather than extrinsic coagulation pathway is unknown. While larger hematoma sizes in lobar ICH may result in greater tissue factor release and subsequent fVII activation, the intrinsic pathway is largely independent of fVII. Additionally, the faster intrinsic coagulation activation in lobar ICH remained significant after adjusting for hematoma size, making hematoma size an unlikely explanation for these findings. Whether these findings are dependent on the recognized positive feedback mechanism that occurs after initial thrombin generation resulting in a "propagation phase" of subsequent thrombin generation via activation of intrinsic coagulation factors IX and XI requires further investigation.

Strengths of our study included the prospective collection of data and multidisciplinary adjudication by consensus process for ICH location. Inherent limitations to our study included its single-center small sample size which also resulted in limited power to assess for HE differences between groups and convenience sampling subjecting our cohort to potential selection bias. Additionally, there was an absence of specific coagulation factor testing and follow-up ROTEM testing. While the rigorous exclusion criteria were indeed a limitation leading to a large exclusion cohort, this was necessary in attempts to look at coagulation differences driven by location alone rather than other confounding factors. Further work is required to externally validate our findings in a larger cohort. If there are indeed coagulation differences between lobar and deep ICH, future investigations may need to assess whether the clinical, radiographic, and laboratory heterogeneity of lobar compared to deep ICH warrants separate hemorrhage reversal treatment paradigms based on ICH location. Whether ROTEM can provide individualized hemorrhage reversal treatment targets after ICH to improve outcomes also needs further investigation.

Conclusions

Functional coagulation differences between lobar and deep ICH using whole-blood coagulation testing requires external validation. ROTEM may provide insight into the potential pathophysiologic differences of coagulopathy in ICH not observed with traditional coagulation testing.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-019-00672-0) contains supplementary material, which is available to authorized users.

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Authors' Contributions

DR contributed to Project design/development, data collection, data analysis, drafting of manuscript. TC contributed to Project design, editing of manuscript. CZ, GW contributed to Project design/development, data collection. ASR, NY, SP, SA, ESC contributed to data collection, editing of manuscript. MSVE, AE, ROF contributed to Project development, editing of manuscript. KD, AB contributed to data analysis, editing of manuscript. JC contributed to Project design/development, data collection, editing of manuscript. EH contributed to Project design, data analysis, editing of manuscript.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

The Columbia University Institutional Review Board approved this study.

Informed Consent

Consent was provided by the patient or the family if the patient did not have capacity to consent.

Publisher's Note

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