Supplemental Material

Risk Factors for CT Angiography Spot Sign in Deep and Lobar Intracerebral Hemorrhage are Shared

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Supplemental Methods

Study Subjects

Consecutive patients with primary intracerebral hemorrhage (ICH) who presented to Massachusetts General Hospital between December 2000 and May 2013 were evaluated.[1] Inclusion criteria were primary ICH and CT angiography (CTA) performed within 72 hours of symptom onset. Exclusion criteria were infratentorial ICH, multiple hemorrhages, primary intraventricular hemorrhage (IVH), and secondary causes of ICH including vascular malformations, aneurysms, neoplasms, trauma, and hemorrhagic transformation of acute infarction.

Clinical data

Demographic data, past medical history, medication use, alcohol and tobacco use, and time of symptom onset were collected through chart review and interviews with patients or their surrogates. Hospital records were reviewed for admission systolic and diastolic blood pressure, Glasgow Coma Scale score, blood glucose, and international normalized ratio (INR) measurements, and time from symptom onset to baseline CTA.

Imaging analysis

ICH location was determined based on admission CT by study neurologists or neuroradiologists blinded to clinical data. Lobar hemorrhage was defined as ICH originating in the cortex or cortico-subcortical junction. Deep ICH was defined as hemorrhage exclusively involving the thalamus, basal ganglia, internal capsule, or deep periventricular white matter.

Hemorrhages involving both territories were specified as mixed ICH and excluded from the analysis.

CTAs were reviewed by two independent readers for the presence of spot sign according to previously published methods.[2] Hematoma volumes were measured semi-automatically using Analyze 10.0 (Mayo Clinic, Rochester, MN) software following previously described protocols.[2] The presence of hematoma expansion was evaluated in a subgroup of subjects with an available follow-up CT. Hematoma expansion was defined as absolute growth >6 mL or a relative increase >33% compared to the baseline CT.[3] Disagreements regarding ICH location and CTA spot sign readings were adjudicated by consensus.

Statistical analysis

Discrete variables are expressed as count (%), and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. International normalized ratio measured on admission was recoded to four categories: ≤1.2, 1.2-2, 2-3, and >3. Following previous studies, missing INR in subjects who were not treated with warfarin were set to 1.[4] The subgroup with INR ≤1.2 was set as the reference category for this covariate. Time to CTA was modeled as a continuous covariate. Cohort characteristics are presented in Supplemental Table I.

Subjects excluded from this study due to lack of CTA, or CTA performed after the first 72 hours had similar characteristics to included individuals (Supplemental Table II).

We tested association of covariates with spot sign presence using logistic regression. Univariable logistic regression was performed to evaluate unadjusted associations between covariates and spot sign, stratified by ICH location. The results of univariable regression are

demonstrated in the Supplemental Table III. Subsequently, multivariable logistic regression was utilized to identify independent associations after accounting for potential confounders. Covariates with $p<0.05$ in univariable analyses were entered into the model and backward elimination was carried out to the level of 0.2. Collinear factors, as measured through the variance inflation factor were removed when appropriate.

Supplemental Table I. Cohort characteristics

	ICH, No. (%)	
Variable	**Deep (n=335)**	**Lobar (n=406)**
Age, mean (SD)	69 (14)	75 (11)
Female	130 (39)	212 (52)
Hypertension	282 (86)	281 (69)
Diabetes mellitus	84 (25)	67 (17)
Hypercholesterolemia	126 (38)	173 (44)
Coronary artery disease	62 (19)	71 (18)
Atrial fibrillation	53 (16)	92 (23)
Previous ICH	13 (4)	26 (7)
Smoking (current)	36 (15)	50 (17)
Warfarin treatment	47 (14)	80 (20)
Antiplatelet treatment	152 (47)	197 (49)
Statin treatment	105 (33)	139 (35)
Admission blood pressure, mean (SD), mmHg		
Systolic	184 (35)	171 (31)
Diastolic	97 (25)	88 (19)
Admission blood glucose, mean (SD), mmol/L	9 (5)	8 (3)
INR category (All subjects)		
≤1.2	275 (82)	308 (76)
>1.2 - <2	29 (9)	30 (7)
≥2 - ≤3	16 (5)	46 (11)
>3	14 (4)	21 (5)
INR category (Subjects treated with warfarin)		
≤1.2	4 (9)	1 (1)
>1.2 - <2	12 (3)	11 (14)
≥2 - ≤3	16 (35)	46 (58)
>3	14 (3)	21 (27)
ICH volume, median (IQR), mL	14 (6-39)	38 (16-73)
Intraventricular extension	166 (52)	145 (37)
IVH volume*, median (IQR), mL	15 (6-35)	8 (3-18)
Time to CTA, median (IQR), hour	5 (3-7)	6 (3-10)
CTA spot sign	76 (23)	102 (25)

CTA, computed tomography angiography; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; SD, standard deviation;

**Only for patients with intraventricular hemorrhage (n=311)*

Supplemental Table II. Comparison between subgroups with available and missing CTA data

	ICH, No (%)		
Variable	**Complete data (n= 741)**	**Missing data (n=179)**	**p**
Age, mean (SD)	72 (13)	71 (12)	0.19*
Female	399 (54)	95 (53)	0.91
Hypertension	563 (77)	139 (78)	0.74
Diabetes mellitus	151 (21)	39 (22)	0.81
Hypercholesterolemia	299 (42)	73 (41)	0.94
Coronary artery disease	133 (18)	31 (18)	0.90
Atrial fibrillation	145 (20)	24 (13)	0.06
Previous ICH	39 (5)	12 (7)	0.59
Antiplatelet treatment	87 (12)	24 (14)	1.00
Warfarin treatment	349 (48)	76 (44)	0.32
Statin treatment	126 (17)	36 (20)	0.38

** t-test*

ICH: intracerebral hemorrhage

Supplemental Table III. Univariable logistic regression of spot sign in ICH

	Deep ICH		Lobar ICH	
Covariate	**OR [95% CI]**	**p**	**OR [95% CI]**	**p**
Age	1.01 [0.99 – 1.03]	0.15	1.02 [0.99 – 1.04]	0.09
Male sex	1.76 [1.02 – 3.10]	0.04	1.63 [1.04 – 2.57]	0.03
Hypertension	1.53 [0.71 – 3.66]	0.3	1.50 [0.91 – 2.53]	0.12
Hypercholesterolemia	1.31 [0.77 – 2.23]	0.31	1.25 [0.79 – 1.96]	0.34
Diabetes mellitus	1.02 [0.55 – 1.82]	0.95	0.75 [0.38 – 1.39]	0.37
Coronary artery disease	1.53 [0.81 – 2.83]	0.17	2.52 [1.46 – 4.32]	0.0008
Atrial fibrillation	2.02 [1.05 – 3.80]	0.03	1.86 [1.12 – 3.08]	0.01
Previous ICH	0.64 [0.10 – 2.48]	0.57	1.36 [0.54 – 3.13]	0.48
Antiplatelet treatment	1.77 [1.05 – 3.01]	0.03	1.66 [1.05 – 2.63]	0.02
Warfarin treatment	3.12 [1.62 – 5.97]	0.0005	3.22 [1.92 – 5.41]	9.0×10^{-6}
Statin treatment	1.38 [0.79 – 2.39]	0.24	1.25 [0.78 – 1.98]	0.35
Admission blood pressure, mmHg **Systolic** **Diastolic**	1.01 [0.99 – 1.01] 1.005 [0.99 – 1.02]	0.12 0.34	1.01 [1.001 – 1.02] 1.004 [0.99 – 1.02]	0.02 0.46
INR (test for trend)	1.74 [1.29 – 2.37]	0.0003	1.76 [1.39 – 2.23]	2.2×10^{-6}
INR category **>1.2 - < 2.0** **>= 2.0 - <= 3.0** **> 3.0**	 2.31 [0.98 – 5.18] 3.42 [1.17 – 9.60] 4.39 [1.44 – 13.37]	 0.04 0.01 0.007	 1.44 [0.58 – 3.28] 2.79 [1.44 – 5.33] 6.45 [2.60 – 16.94]	 0.4 0.001 7.7×10^{-5}
Intraventricular extension	2.67 [1.53 – 4.79]	0.0007	2.21 [1.38 – 3.53]	0.0009
ICH volume, per 10 mL	1.21 [1.13 – 1.31]	3.7×10^{-7}	1.19 [1.12 – 1.26]	2.4×10^{-9}
Time to CTA	0.85 [0.77 – 0.93]	0.0006	0.94 [0.89 – 0.98]	0.003

CI, confidence interval; CTA, computed tomography angiography; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; IVH, intraventricular hemorrhage; mL, milliliter; OR, odds ratio

References

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