The Effect of Aging and Small-Vessel Disease Burden on Hematoma Location in Patients with Acute Intracerebral Hemorrhage

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Keywords

Intracerebral hemorrhage · Aging · Etiology · Magnetic resonance imaging · Small-vessel disease

Abstract

Introduction: Intracerebral hemorrhage (ICH) is a devastating hemorrhagic event and is associated with high mortality or severe neurological sequelae. Age-associated differences in hematoma location for nonlobar ICH are not well known. The aims of the present study were to elucidate the relationship between age and hematoma location and to assess the differences in small-vessel disease (SVD) burden as a potential surrogate marker for longstanding hypertension among various hematoma locations. **Methods:** From September 2014 through July 2019, consecutive patients with acute, spontaneous ICH were retrospectively enrolled from a prospective registry. Magnetic resonance imaging was performed during admission, and the total SVD burden score (including microbleeds, lacunes, enlarged perivascular spaces, and white matter hyperintensities) was calculated. The relationships of hematoma location with aging and SVD burden were assessed by using multivariate logistic regression

analyses. **Results:** A total of 444 patients (156 women [35%]; median age 69 [interquartile range 59–79] years; National Institutes of Health Stroke Scale score 9 [17][3–17]) were enrolled in the present study. Multivariate logistic regression analyses showed that advanced age was independently associated with thalamic (odds ratio [OR]: 1.48, 95% confidence interval [CI]: 1.19–1.84, $p < 0.001$ for 10-year increment) and lobar hemorrhage (OR: 1.58, 95% CI: 1.19–2.09, $p = 0.002$) and was independently and negatively related to putaminal hemorrhage (OR: 0.55, 95% CI: 0.44–0.68, $p < 0.001$). The total SVD burden score was independently and positively associated with thalamic hemorrhage (OR: 1.27, 95% CI: 1.01–1.59, $p = 0.045$) and negatively with lobar hemorrhage (OR: 0.74, 95% CI: 0.55–0.99, $p = 0.042$), even after adjusting by age, but not with putaminal hemorrhage (OR: 0.91, 95% CI: 0.73–1.14, $p = 0.395$). **Conclusion:** Putaminal, thalamic, and lobar hemorrhages are prone to occur in specific ages and SVD states: putaminal in young patients, thalamic in old and high SVD burden patients, and lobar hemorrhages in old and low SVD burden patients. Susceptibility to bleeding with aging or severe SVD accumulation seems to differ considerably among brain locations.

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Introduction

Intracerebral hemorrhage (ICH) is a devastating hemorrhagic event that is associated with high mortality and severe neurological sequelae [1]. The incidence of ICH rises with age, and although the annual incidence of ICH has decreased through the past few decades, the absolute number of patients has increased, especially elderly individuals in developed countries [2]. The mean age of patients with first-ever ICH is rising [2], and the number of old ICH patients is predicted to continue to rise [3]. Elderly ICH patients had more baseline comorbidities and antithrombotic treatments, and mortality was higher than for young ICH patients [3–7]. To establish appropriate management strategies for elderly ICH patients is one of the future challenges [8].

Understanding the clinical characteristics and mechanisms of elderly ICH patients is one of the bases for developing approaches for such patients. Clinical features of ICH, in terms of hematoma volume, hematoma location, and blood pressure (BP) at onset, are considered to differ between young and old ICH patients [9, 10]. Lobar hemorrhage is reported to increase in elderly patients, mainly in association with cerebral amyloid angiopathy (CAA) [11]. However, age-associated differences in hematoma location for nonlobar ICH are not well known. A few past studies suggested that thalamic or cerebellar hemorrhage was more frequently observed than putaminal hemorrhage in aged ICH patients [6, 7, 10, 12], but almost all of the results were from univariate analyses. Elucidating the relationship between aging and hematoma location can be a clue for developing age-specific ICH prevention and treatment strategy; indeed, some hemorrhage locations including thalamus were reported to be associated with worse outcomes [13]. We hypothesized that thalamic hemorrhage is more frequent as age advances because thalamic hemorrhage occurs based on longstanding hypertension, whereas putaminal hemorrhage is based on an abrupt BP increment [14]. Cerebral small-vessel disease (SVD) due to microangiopathies not related to CAA is known to be caused by longstanding hypertension [15, 16], and it is reported to increase with age [17], but the association between SVD and hematoma location has not been well studied. The aims of the present study were to elucidate the relationship between age and hematoma location and to assess the differences in SVD burden as a potential surrogate marker for longstanding hypertension in various hematoma locations.

Methods

Subjects

From September 2014 through July 2019, consecutive patients with acute (<7 days from onset), spontaneous ICH admitted to our stroke unit (SU) were retrospectively enrolled from a prospective registry [18]. Patients with secondary ICH and pure intraventricular hemorrhage were excluded. This study was approved by the institutional Ethics Committee (No. 26-10-398). Written, informed consent was obtained from all patients or their next of kin.

Clinical Characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and past medical history, were recorded on admission. Cardiovascular risk factors were defined as follows: (1) hypertension, history of using antihypertensive agents, systolic BP ≥ 140 mm Hg, or diastolic BP ≥ 90 mm Hg before or ≥ 2 weeks after stroke onset; (2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥ 200 mg/dL, or glycosylated hemoglobin $\geq 6.5\%$ on admission; (3) hyperlipidemia, use of antihyperlipidemic agents, serum total cholesterol level ≥ 220 mg/dL, or low-density lipoprotein cholesterol level ≥ 140 mg/dL; (4) current smoker; and (5) daily alcohol intake. Neurological severity was assessed by using the National Institutes of Health Stroke Scale (NIHSS), and functional outcomes were evaluated by using the modified Rankin scale (mRS). Anthropometric measurements and routine blood biochemistry examinations were performed on admission. Hematoma location was classified by 2 experienced stroke neurologists (Y.S. and T.S.) by consensus as putamen, thalamus, lobar, caudate, brainstem, and cerebellum. When a hematoma occupied >1 location, the hematoma location was determined to be the one that contained the largest portion of the hematoma. Hematoma volume was evaluated with non-contrast computed tomography on admission by using the ABC/2 method.

Calculating Total SVD Burden Score

Multimodal 1.5-T magnetic resonance imaging (MRI, Echelon Oval; Hitachi Medical Systems, Tokyo, Japan) including fluid-attenuated inversion recovery (TR/TE, 10,000/120 ms; TI, 2,500 ms; field of view, 24 cm; acquisition matrix, 288×224 ; and slice thickness, 4.5 mm, with a 2.5-mm intersection gap), T2-weighted imaging (TR/TE 4,200/117.52 ms), and T2*-weighted imaging (TR/TE, 480/18 ms; field of view, 24 cm; acquisition matrix, 256×204 ; and slice thickness, 4.5 mm, with a 2.5-mm intersection gap) was performed during admission. The imaging evidence of SVD was assessed based on the presence and severity of white matter hyperintensities (WMHs), cerebral microbleeds, lacunes, and enlarged perivascular spaces. These changes were assessed based on the Standards for Reporting Vascular Changes in Neuroimaging (STRIVE) criteria [19]. The severity of WMHs was assessed by using the Fazekas scale [20], the severity of enlarged perivascular spaces was scored by using a semiquantitative score [21], and these scores were evaluated on the side contralateral to the hematoma. To assess the association between SVD and hematoma location, the total SVD burden score [22] (0–4) was calculated by adding 1 point for each SVD feature: severe periventricular (Fazekas grade 2 or 3) and/or deep WMHs (Fazekas grade 3); presence of microbleed; presence of lacune; and prominent enlarged perivas-

Table 1. Baseline clinical characteristics by age-group

Variable	Total (<i>n</i> = 444)	Young (<65 yrs) (<i>n</i> = 161)	Young-old (65–74 yrs) (<i>n</i> = 130)	Old-old (75–84 yrs) (<i>n</i> = 100)	Oldest-old (≥85 yrs) (<i>n</i> = 53)	<i>p</i> value
Female sex, <i>n</i> (%)	156 (35)	30 (19)	39 (30)	53 (53)	34 (64)	<0.001
Body mass index, median (IQR), kg/m ²	22.4 (20.3–25.1)	24.7 (21.7–28.2)	23.0 (20.9–25.1)	21.2 (19.0–23.1)	21.3 (19.1–23.4)	<0.001
Prior history of ischemic stroke, <i>n</i> (%)	46 (10)	14 (9)	11 (9)	14 (14)	7 (13)	0.411
Prior history of hemorrhagic stroke, <i>n</i> (%)	36 (8)	16 (10)	7 (5)	12 (12)	1 (2)	0.078
Prior history of vascular disease, <i>n</i> (%)	22 (5)	4 (3)	2 (2)	14 (14)	2 (4)	<0.001
Vascular risk factors, <i>n</i> (%)						
Hypertension	378 (85)	139 (86)	113 (87)	87 (87)	39 (74)	0.095
Diabetes mellitus	81 (18)	27 (17)	28 (22)	17 (17)	9 (17)	0.719
Hyperlipidemia	124 (28)	49 (30)	30 (23)	35 (35)	10 (19)	0.083
Current smoking	139 (31)	74 (46)	41 (32)	22 (22)	2 (4)	<0.001
Daily alcohol intake	228 (51)	109 (68)	70 (54)	35 (35)	14 (26)	<0.001
Premorbid antithrombotic treatment, <i>n</i> (%)	105 (24)	18 (11)	36 (28)	34 (34)	17 (32)	<0.001
Preadmission mRS score, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–3)	<0.001
Systolic BP on arrival, median (IQR), mm Hg	184 (163–208)	190 (171–210)	177 (158–194)	182 (158–203)	169 (141–205)	0.003
Diastolic BP on arrival, median (IQR), mm Hg	102 (90–116)	110 (100–123)	100 (89–112)	96 (84–110)	93 (78–107)	<0.001
Initial NIHSS score, median (IQR)	9 (3–17)	10 (4–15)	5 (2–14)	7 (2–14)	6 (1–20)	0.131
Hematoma location, <i>n</i> (%)						
Putamen	158 (36)	87 (54)	40 (31)	19 (19)	12 (23)	<0.001
Thalamus	156 (35)	42 (26)	54 (42)	39 (39)	21 (40)	0.026
Lobar	78 (18)	13 (8)	20 (15)	32 (32)	13 (25)	<0.001
Caudate nucleus	7 (2)	2 (1)	1 (1)	2 (2)	2 (4)	0.489
Brainstem	24 (5)	14 (9)	5 (4)	3 (3)	2 (4)	0.143
Cerebellum	21 (5)	3 (2)	10 (8)	5 (5)	3 (6)	0.134
Initial hematoma volume, median (IQR), mL	8.2 (3.2–21.8)	9.5 (3.6–21)	7.2 (2.7–15)	7.0 (3.2–22)	7.4 (3.0–14)	0.235
Biochemistry sign at admission, median (IQR)						
Hemoglobin, g/dL	13.9 (12.6–15.1)	14.8 (13.7–15.6)	14.4 (13.2–15.4)	13.3 (11.9–14.1)	11.9 (10.9–13.7)	<0.001
Platelet count, 10 ⁴ /μL	21.0 (17.4–25.0)	22.2 (19.1–27.3)	20.4 (17.5–23.4)	19.6 (16.9–24.6)	20.6 (14.8–26.2)	0.001
Total cholesterol, mg/dL*	190 (166–216)	195 (174–221)	188 (166–209)	180 (159–208)	184 (158–224)	0.033
eGFR, mL/min	69 (57–83)	74 (60–88)	69 (59–84)	62 (51–73)	58 (40–78)	<0.001
mRS score at discharge, median (IQR)	4 (2–5)	3 (2–4)	4 (2–5)	4 (3–5)	4 (3–5)	0.010

mRS, modified Rankin scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; eGFR, estimated glomerular filtration rate; IQR, interquartile range. * Data missing in 20 patients.

cular space (grades 2–4) in the basal ganglia. Each component of the total SVD burden score was assessed by Y.S. and S.S. separately for calculating inter-rater reliability and then decided by consensus in cases of nonagreement.

Statistical Analyses

All patients were divided into 4 groups based on their age at ICH onset: young (<65 years), young-old (65–74 years), old-old (75–84 years), and oldest-old (≥85 years). First, clinical background characteristics were compared among the 4 groups by using univariate analyses. Second, the associations between hematoma locations and advanced age were analyzed by using multivariate logistic regression analyses with a backward stepwise selection procedure. Each hematoma location was entered as a dependent variable, and variables shown in Table 1 (except the NIHSS and mRS score at discharge because these variables were consequences of, rather than factors associated with, hematoma location) were included in the models as independent variables, and a backward selection procedure was performed using $p > 0.1$ of the likelihood ratio test for exclusion. Next, to assess the effect of SVD burden on hematoma location, clinical characteristics including the total SVD burden score were compared among putaminal, tha-

lamic, lobar, and other location (caudate, brainstem, and cerebellum) hemorrhage patients. Patients with caudate, brainstem, and cerebellar hemorrhage were analyzed together due to their small sample size. Finally, multivariate logistic regression analyses were performed to identify independent factors associated with various hematoma locations. All variables identified on univariate analyses with values of $p < 0.1$ including total SVD burden score, but not the initial NIHSS score and diastolic BP, were entered into the models. The initial NIHSS score was excluded because this variable was a consequence of, rather than a factor associated with, hematoma location. Diastolic BP was excluded because it was highly correlated with systolic BP. The relationship between hematoma location and the total SVD burden score was also tested in first-ever stroke patients. Moreover, because ICH due to CAA was not completely ruled out in the present study and the association between CAA and microbleeds, especially strictly lobar microbleeds, was reported [23, 24], multivariate analyses using the modified SVD score which removed the effect of microbleeds or strictly lobar microbleeds (SVD score only for enlarged perivascular space, WMH, and lacune, or not add 1 point for microbleeds when microbleed was located only in lobar, respectively) were conducted, for sensitivity analysis. The relative risks for specific hematoma locations

Table 2. Results of binary logistic regression models for factors associated with (a) putaminal hemorrhage, (b) thalamic hemorrhage, and (c) lobar hemorrhage

Variable	OR (95% CI)	<i>p</i> values
a Putaminal hemorrhage		
Age, per 10 years	0.55 (0.44–0.68)	<0.001
Body mass index, per 1 kg/m ²	0.95 (0.89–1.01)	0.078
Hypertension	0.53 (0.25–1.13)	0.100
Premorbid antithrombotic treatment	0.59 (0.33–1.08)	0.088
Preadmission mRS	1.30 (1.04–1.63)	0.020
Hematoma volume, per 10 mL	1.11 (1.02–1.20)	0.011
b Thalamic hemorrhage		
Age, per 10 years	1.48 (1.19–1.84)	<0.001
Past history of vascular disease	5.01 (1.51–16.6)	0.009
Systolic BP on arrival, per 10 mm Hg	1.09 (1.00–1.17)	0.038
Hematoma volume, per 10 mL	0.57 (0.46–0.70)	<0.001
Hemoglobin, per 1 g/dL	1.13 (0.99–1.29)	0.058
Platelet count, per 10 ⁴ /μL	1.05 (1.01–1.09)	0.014
c Lobar hemorrhage		
Age, per 10 years	1.58 (1.19–2.09)	0.002
Female sex	2.43 (1.27–4.66)	0.008
Body mass index, per 1 kg/m ²	1.13 (1.04–1.22)	0.003
Hypertension	2.24 (1.04–4.79)	0.003
Systolic BP on arrival, per 10 mm Hg	0.85 (0.77–0.94)	0.002
Hematoma volume, per 10 mL	1.36 (1.22–1.51)	<0.001
Total cholesterol, per 100 mg/dL	0.51 (0.24–1.08)	0.078

The variables identified by the backward selection procedure are listed. OR, odds ratio; CI, confidence interval; mRS, modified Rankin scale; BP, blood pressure.

are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Univariate analyses were performed by using the χ^2 test, Fisher's exact test, or the Mann-Whitney *U* test, as appropriate. The data are presented as median values (interquartile range [IQR]) or numbers (%). All statistical analyses were performed by using SPSS version 23.0 software (IBM SPSS Inc., Armonk, NY, USA). Results were considered significant at $p < 0.05$.

Data Availability

Data are available upon reasonable request.

Results

Overall, 464 consecutive patients with ICH were admitted to our SU during the study period. Of these, 16 patients diagnosed as having secondary ICH due to cerebral neoplasms, bleeding diathesis, arteriovenous malformations, moyamoya disease, infective endocarditis, minor trauma, or cerebral venous thrombosis were excluded. Four patients were also excluded due to pure intraventricular hemorrhage. Finally, 444 patients (156 women [35%]; median age, 69 [IQR 59–79] years; NIHSS score, 9 [3–17]; median time from symptom onset to admission,

2.60 [1.01–12.0] hours) were enrolled in the present study (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515411). Of these 444 patients, 161 (36%) were classified as the young group, 130 (29%) were in the young-old group, 100 (23%) were in the old-old group, and 53 (12%) were in the oldest-old group. Table 1 shows the baseline clinical characteristics of the 4 groups. The proportions of female sex ($p < 0.001$), having a prior history of vascular disease ($p < 0.001$), current smoker ($p < 0.001$) and drinker ($p < 0.001$), and receiving premorbid antithrombotic treatment ($p < 0.001$), as well as the values of the body mass index ($p < 0.001$), preadmission mRS score ($p < 0.001$), time from onset to admission ($p = 0.011$), systolic ($p = 0.003$) and diastolic ($p < 0.001$) BPs, laboratory data, and mRS score at discharge ($p = 0.010$), were significantly different among the 4 groups. The rate of putaminal hemorrhage tended to decrease, whereas thalamic and lobar hemorrhages tended to increase with advanced age ($p = 0.026$, Fig. 1). Multivariate logistic regression analyses showed that advanced age was independently and negatively associated with putaminal hemorrhage (OR: 0.55, 95% CI: 0.44–0.68 for 10-year increment, $p < 0.001$, Table 2a), and positively with thalam-

Table 3. Multivariate logistic regression model for associated factors with putaminal, thalamic, and lobar hemorrhages

Independent variable	Dependent variable					
	putaminal hemorrhage		thalamic hemorrhage		lobar hemorrhage	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Female sex	1.08 (0.60–1.94)	0.798	1.41 (0.78–2.56)	0.260	1.28 (0.63–2.59)	0.491
Age, per 10 years	0.59 (0.47–0.76)	<0.001	1.23 (0.96–1.57)	0.095	1.58 (1.16–2.16)	0.004
Hypertension	0.49 (0.23–1.04)	0.064	1.29 (0.63–2.63)	0.489	1.87 (0.85–4.07)	0.118
Current smoking	0.75 (0.43–1.31)	0.313	1.37 (0.78–2.42)	0.278	0.98 (0.46–2.11)	0.968
Daily alcohol intake	1.76 (1.02–3.04)	0.044	1.13 (0.64–1.98)	0.681	0.58 (0.29–1.15)	0.117
Premorbid antithrombotic treatment	0.53 (0.27–1.05)	0.067	1.11 (0.61–2.02)	0.742	1.34 (0.64–2.80)	0.435
Systolic BP on arrival, per 10 mm Hg	0.95 (0.87–1.03)	0.186	1.05 (0.97–1.15)	0.216	0.90 (0.81–0.99)	0.039
Hematoma volume, per 10 mL	1.06 (0.97–1.17)	0.201	0.50 (0.38–0.67)	<0.001	1.43 (1.26–1.63)	<0.001
Hemoglobin, per 1 g/dL	1.00 (0.86–1.15)	0.966	1.05 (0.91–1.22)	0.495	0.99 (0.83–1.18)	0.915
Total SVD score, per 1 point	0.91 (0.73–1.14)	0.395	1.27 (1.01–1.59)	0.045	0.74 (0.55–0.99)	0.042

BP, blood pressure; SVD, small-vessel disease; OR, odds ratio; CI, confidence interval.

Fig. 1. Relative hematoma location by patients' age at ICH onset. ICH, intracerebral hemorrhage.

ic hemorrhage (OR: 1.48, 95% CI: 1.19–1.84, $p < 0.001$, Table 2b) and lobar hemorrhage (OR: 1.58, 95% CI: 1.19–2.09, $p = 0.002$, Table 2c). The rate of putaminal hemorrhage seemed to decrease steeply with age, whereas the proportions of thalamic and lobar hemorrhages seemed to increase in young-old and old-old or older groups, respectively (Fig. 1). No significant relationships were found between advanced age and caudate, brainstem, and cerebellar hemorrhages.

Next, to assess the effect of SVD burden on hematoma location, clinical characteristics were compared among

patients with different hematoma locations (online suppl. Table 1, 2). Proportion of female sex ($p = 0.002$), having hypertension ($p = 0.024$), current drinker ($p = 0.001$), patients who received premorbid antithrombotic treatment ($p = 0.036$), values of age ($p < 0.001$), time from ICH onset to admission ($p < 0.001$), systolic ($p = 0.018$) and diastolic ($p = 0.015$) BPs, NIHSS score ($p < 0.001$), hematoma volume ($p < 0.001$), and initial hemoglobin ($p = 0.006$) were different among various hematoma locations. MRI was performed in 344 of 444 (77%) patients during admission, a median of 1 day (IQR 1–5 days) from onset. The inter-rater reproducibility for each SVD feature showed moderate to good (Cohen's kappa statistics: presence of microbleed[s], 0.65; presence of lacune[s], 0.62; prominent perivascular space, 0.50; and severe WMH, 0.64) agreement. Each SVD marker tended to differ among various hematoma locations, especially WMH and microbleed (online suppl. Table 2). The total SVD burden score was also different among various hematoma locations ($p < 0.001$), and multivariate logistic regression analysis showed that the total SVD burden score was independently associated with thalamic hemorrhage (OR: 1.27, 95% CI: 1.01–1.59, $p = 0.045$ for 1-point increment, Table 3), even after adjusting by age. The total SVD burden score was independently and negatively related to lobar hemorrhage (OR: 0.74, 95% CI: 0.55–0.99, $p = 0.042$) and showed a nonsignificant tendency for a negative association with putaminal hemorrhage (OR: 0.91, 95% CI: 0.73–1.14, $p = 0.395$, Table 3) on multivariate analyses. Indeed, the proportion of thalamic hemorrhage rose and the rate of lobar hemorrhage decreased as the total SVD burden score increased in the total cohort and most sub-

Fig. 2. Distribution of hematoma locations according to the total SVD burden score in all patients (**a**) and age-stratified subgroups (**b**). SVD, small-vessel disease. *Others include caudate, brainstem, and cerebellar hemorrhages.

groups (Fig. 2; online suppl. Fig. 2), although some subgroups had only a few patients. The independent associations between advanced age and putaminal (OR: 0.52, $p < 0.001$), thalamic (OR: 1.60, $p < 0.001$), and lobar (OR: 1.77, $p \leq 0.001$) hemorrhages and the independent relationship between the total SVD burden score and thalamic (OR: 1.42, $p = 0.006$) hemorrhage were not changed when analyzing only patients with first-ever stroke (those without a past history of stroke, $n = 366$). SVD score without microbleeds component was not associated with hematoma locations, but modified SVD score was independently related to thalamic (OR: 1.29, $p = 0.029$) and lobar (OR: 0.73, $p = 0.029$) hemorrhages, when using modified SVD score which removed the effect of lobar microbleeds (online suppl. Table 3).

Discussion

The present study showed that putaminal hemorrhage was independently and negatively related to advanced age, whereas advanced age was an independent factor associated with thalamic and lobar hemorrhages in consecutive patients with acute, spontaneous ICH. Cerebral SVD burden had a positive correlation with thalamic hemorrhage but a negative association with lobar hemorrhage. Advanced age was an independent factor associated with putaminal, thalamic, and lobar hemorrhages. These associations between aging and relative increase or decrease in specific brain locations of hemorrhage have been little known previously, except for lobar hemorrhage, probably because few old patients were included in the previous study [4]. A few past studies reported that patients with thalamic hemorrhage were older than those with putaminal hemorrhage, but almost all of the results were from univariate analyses [6, 7, 10, 12]. One more possible explanation is that most of the past studies treated thalamic and putaminal hemorrhages together as “deep” ICH [25]. Putaminal hemorrhage occurs in young patients (mainly <65 years), whereas thalamic or lobar hemorrhage develops in old patients (from the results of the present study, older than 65 years for thalamic hemorrhage and older than 75 years for lobar hemorrhage, Fig. 1), and considering thalamic and putaminal hemorrhages together as deep ICH should be done cautiously, especially when evaluating factors related to aging.

The prevalence and severity of SVD are also known to increase with age [17], so we hypothesized that SVD burden was associated with thalamic or lobar hemorrhage.

Interestingly, the total SVD burden score was independently associated with thalamic hemorrhage even after adjusting for age, and, surprisingly, significantly and negatively related to lobar hemorrhage. The total SVD score tended to be negatively associated with putaminal hemorrhage. Indeed, the proportion of thalamic hemorrhage grew and that of putaminal or lobar hemorrhage decreased as the total SVD burden score increased in most age-stratified subgroups (Fig. 2 and online suppl. Fig. 2). SVD burden can be used as an imaging predictor for thalamic and lobar hemorrhages.

The occurrence of hypertensive ICH is considered to be biphasic, with patients presenting both at the onset of hypertension and later, after developing considerable wear and tear on penetrating brain arteries [14]. Later in the course of hypertension, degenerative changes including fibrinoid necrosis, lipohyalinosis, or microaneurysms develop, leading to the typical imaging features of SVD [16]. SVD burden can serve as imaging evidence for the duration of hypertension [15, 16], and the results of the present study may indicate that putaminal hemorrhage is prone to occur during the initial course of hypertension (young and low SVD burden), whereas, after a considerable hypertensive period during which enough SVD pathology can accumulate (old and high SVD burden), hypertensive hemorrhage is frequently observed in the thalamus. On the contrary, patients with CAA, which often causes lobar hemorrhage, have less history of hypertension and show lower BPs at ICH onset than those with hypertensive ICH [26]. Lobar ICH attributed to CAA is considered to develop after adequate amyloid deposition in the vessel wall [27], usually in the nonhypertensive state (old but low SVD burden). Age and SVD burden may predict the locations of hematomas in spontaneous ICH patients. Although the precise mechanisms for the differences in susceptibility to bleed according to age or SVD among various brain locations are unclear, hemodynamic differences originating from vascular anatomy [28] or differences in sensitivity to chronic hypertension or aging [29] may account for the heterogeneity.

The strengths of the present study included the relatively large number of spontaneous ICH patients, recruiting many oldest-old patients, and MRI acquisition in the acute phase of ICH. However, there are some limitations to be addressed. First, because of the cross-sectional nature of the study design, the results of the present study showed associations, not causal relationships. Moreover, this study showed only relative increases or decreases of specific hematoma locations by patients' age or SVD bur-

den in the ICH cohort, not absolute increases or decreases. Second, due to the retrospective study design, whether and when to perform head MRI was left to the attending physicians' discretion. Consecutive patients with acute, spontaneous ICH were included in the present study, but MRI information (including total SVD burden score) was available in only 77% (344 of 444 patients) of the patients. Third, although the total cohort was relatively large, some subgroups were very small (Fig. 2). Fourth, almost all of the patients included in the present study were Asian, so the results may not be generalizable to all ICH patients; indeed, most of the past studies that showed that patients with thalamic hemorrhage were older than those with putaminal hemorrhage were from Asian countries [7, 10, 12]. The results of the present study generate hypotheses, rather than showing causal relationships. The present results should be confirmed by a large-scale prospective study including patients of varied ethnic backgrounds to investigate the causal relationships between hematoma location and advanced age or SVD burden.

In conclusion, putaminal, thalamic, and lobar hemorrhages tend to occur at specific ages and in specific SVD states: putaminal in young and low SVD burden; thalamic in old and high SVD burden; and lobar in old and low SVD burden. The combination of age and SVD burden was associated with hematoma location. Susceptibility to bleeds in the early or longstanding phase of hypertension seems to be considerably different among brain locations, even between the putamen and thalamus, which are both supplied by perforating arteries and often regarded together as deep ICH when hemorrhage occurs. Unraveling the underlying mechanisms of this heterogeneity is urgently needed for better understanding and developing future prevention strategies for ICH.

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Statement of Ethics

This study was approved by the institutional Ethics Committee (No. 26-10-398). Written, informed consent was obtained from all patients or their next of kin.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Yuki Sakamoto: designed and conceptualized the study, analyzed the data, conducted statistical analyses, and drafted the manuscript. Takahiro Sato: analyzed the data. Chikako Nito: interpreted the data. Yasuhiro Nishiyama: interpreted the data. Satoshi Suda: played a major role in the acquisition of the data. Noriko Matsumoto: played a major role in the acquisition of the data. Junya Aoki: played a major role in the acquisition of the data. Tomonari Saito: played a major role in the acquisition of the data. Kentaro Suzuki: played a major role in the acquisition of the data. Takehiro Katano: played a major role in the acquisition of the data. Kazumi Kimura: played a major role in the acquisition of the data.

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