Location and timing of recurrent, non-traumatic intracerebral hemorrhage

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Abstract

Importance: The spatial and temporal distribution of intracerebral hemorrhage (ICH) recurrence are largely unknown.

Objective: To assess timing and location of recurrent ICH events in relation to the index ICH event (adjacent [$_{adj}$ICH] versus remote [$_{rem}$ICH]).

Design: Pooled analysis of individual cohort studies (2002-2021). Data analysis was performed 12/2023 to 12/2024.

Setting: Hospital-based European cohorts.

Participants: Patients with ≥2 clinically distinguishable (≥ 1 recurrent) small-vessel disease-related ICH events.

Exposures: ICH location, underlying small vessel disease type.

Main outcomes and measures: The primary outcome was $_{adj}$ICH, defined by anatomical ICH location and side, secondary outcome was time to recurrence. We performed multivariable regression analyses adjusting for ICH location, cerebral amyloid angiopathy (CAA; according to Boston 2.0 or simplified Edinburgh criteria), convexity subarachnoid hemorrhage (cSAH) extension, hypertension and antihypertensive treatment, including an interaction term for hypertension and antihypertensive treatment.

Results: We included 733 patients (median age 72.4 years, IQR 65.2-79, 47.2% female) with 1616 ICH events (733 index, 883 recurrent ICH; range 1-6 recurrences) over a median follow-up of 2.5 years (IQR 0.7-4.9). 340 patients (46.4%) had $_{adj}$ICH and 393 patients (53.6%) had $_{rem}$ICH. Of 883 recurrent ICH events, 476 occurred adjacent to the index ICH and 407 in remote brain areas. In multivariable regression analyses, lobar index ICH (aOR 2.11, 95% CI 1.35-3.29) and CAA at index ICH (aOR 2.34, 95% CI 1.69-3.26) were associated with higher odds of $_{adj}$ICH, while cerebellar index ICH was associated with lower odds of $_{adj}$ICH (aOR 0.24, 95% CI 0.07-0.84). For patients with $_{adj}$ICH, the median time to recurrence was 1.25 years (IQR 0.36-3.38), while it was 2.21 years (IQR 0.66-4.85) for $_{rem}$ICH. Previous lobar or cSAH (Coef. -0.65, 95% CI -1.14 to -0.15, p=0.01) and the number of previous ICH (Coef. -0.53, 95% CI -0.81 to -0.24, p<0.001) were independently associated with a shorter time to recurrence, while

anticoagulation on admission was associated with a longer time to recurrence (Coef. 0.73, 95% CI 0.06-1.39, p=0.033).

Conclusions and relevance: This study identified $_{adj}$ICH as a phenomenon associated with early recurrence and CAA. This suggests regional tissue-based factors that may facilitate recurrence. Identifying and targeting local vasculopathic changes may represent potential novel treatment targets.

Key points

Question: What is the spatial and temporal distribution of recurrent intracerebral hemorrhage (ICH) events?

Findings: In this multi-cohort collaboration analysis including 733 patients with 1616 ICH events, 340 patients (46.4%) had recurrent ICH located adjacent to a previous ICH ($_{adj}$ICH). Features of cerebral amyloid angiopathy were associated with $_{adj}$ICH. Time to recurrence was shorter in patients with $_{adj}$ICH (1.25 years, IQR 0.36-3.38) compared to patients who had recurrent ICH remote to a previous ICH (2.21 years, IQR 0.66-4.85).

Meaning: $_{adj}$ICH is a phenomenon associated with early recurrence and features of CAA. The spatial and temporal clustering suggests regional tissue-based factors may play a role.

Introduction

Intracerebral hemorrhage (ICH) is a disease causing significant morbidity and mortality[1,2]. The incidence of ICH is projected to increase significantly in Europe by 2050[3].

Cerebral small vessel disease is the major cause of non-traumatic ICH in elderly[4,5], likely responsible for >80% of cases. There are two major types of small vessel diseases – cerebral amyloid angiopathy (CAA) and hypertension-associated deep perforator arteriolopathy, which may be concomitantly present in many patients with ICH based on findings from histopathology[6] and MRI studies[7]. Both types of small vessel diseases affect different areas of the brain, and local and regional disease burden may vary. Survivors of ICH are at risk of recurrent ICH[8]. Historical data of unselected patients with ICH found annualized rates of recurrence between 1.7% and 7.4%[8], while contemporary cohorts reported highest recurrence rates in CAA[7,9,10]. However, the exact mechanisms associated with frequent and/or early recurrences remain largely unknown.

In our clinical practice, we often observed patients with recurrent ICH in spatial and/or temporal proximity to a previous ICH event. The primary aim of this study was to investigate the frequency of recurrent ICH events in brain regions adjacent to an index ICH event ($_{adj}$ICH, compared to ICH located in other brain regions, i.e. remote ICH, $_{rem}$ICH). Secondary aims were to assess time to recurrence and identify factors associated with $_{adj}$ICH.

Methods

Study setting

The European Intracerebral Hemorrhage Recurrence Alliance (EURECA) is a multicenter collaboration of local registries or cohort studies. Cohorts for the EURECA collaboration were identified through existing networks and prior collaborations. We pooled individual patient data of patients with recurrent, non-traumatic ICH and convexity subarachnoid hemorrhage (cSAH). A detailed overview of all 14 participating cohorts including data from 20 centers is available in supplemental table S1. Patients were eligible if they had imaging-documented, recurrent, non-traumatic ICH/cSAH with available clinical and imaging information about the index and recurrent ICH events. We defined recurrent ICH as a new, clinically apparent ICH detected on follow-up brain imaging which was independent from the index ICH event in time and space. Clinical deterioration due to secondary hematoma expansion of the index ICH does not fulfill the criteria for recurrent ICH. Diagnostic work-up was performed according to international guidelines[11,12] and a commonly used prediction score[13] to identify macrovascular causes of ICH including non-invasive CT/MR-angiography or digital subtraction angiography if deemed necessary by local investigators. We excluded patients with ICH due to a secondary cause, i.e. macrovascular or structural brain lesion. The manuscript was prepared in line with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement[14].

Data collection

Clinical data collection

All data were collected as part of the respective primary cohort by local investigators. Anonymised data from all cohorts was sent to the coordinating center (Inselspital Bern, Switzerland). We assessed clinical and neuroimaging data, including demographics (age, sex, date of event); cerebrovascular risk factors and comorbidities (history of hypertension, diabetes, dyslipidemia, atrial fibrillation); medication on admission (antiplatelet treatment, anticoagulants, antihypertensive treatment, glucose-lowering treatment, lipid-lowering treatments) and clinical presentation on admission (NIHSS, GCS, systolic and diastolic blood pressure). The total follow-up period was defined as the time from the index ICH to the last documented follow-up ICH.

Neuroimaging data collection

For every single event, local investigators assessed ICH locations in their cohort according to the Cerebral Hemorrhage Anatomical Rating InStrument (CHARTS), which has been shown to have excellent interrater reliability[15]. We determined the presence of CAA according to the simplified Edinburgh CT criteria (high probability of CAA based on the presence of finger-like

projections AND subarachnoid hemorrhage)[6] or the Boston MRI criteria (definite or probable CAA based on the criteria of version 1.5 or 2.0, depending on the timepoint of data collection)[16,17]. If a patient had multiple hemorrhages at the same timepoint, we considered the largest haematoma as the epicentre and used this location for this analysis.

Outcomes

The prespecified primary outcome was recurrent ICH adjacent to any previous one ($_{adj}$ICH), defined as ICH in the same brain region and side using the CHARTS[15] classification tool, versus remote ICH ($_{rem}$ICH), defined as recurrent ICH in brain regions distant from a previous ICH i.e. if a patient had more than one recurrence with at least one recurrent ICH adjacent to a previous one (not necessarily the index ICH), we grouped this patient into the $_{adj}$ICH group. Secondary outcomes were time to recurrence from the previous to the next ICH, and ICH location according to CHARTS[15].

Statistical analysis

Data management and statistical analysis were performed by MBG using STATA MP 16.0 (Stata Corp.). The statistical analysis plan, including the selection of co-variables, was developed by MBG and DJS prior to receiving any data from collaborators. For descriptive analyses, we grouped patients according to the presence or absence of the primary outcome, $_{adj}$ICH, and compared groups using appropriate descriptive statistics. We reported percentages and 95% confidence intervals (95% CIs) for binary and categorical variables, and median and interquartile range (IQR) for continuous, non-normally distributed outcomes. Given that this was an exploratory analysis, there was no formal hypothesis testing and we did not adjust for multiple testing. All regression analyses were performed using listwise deletion (cases with missing values were excluded from the regression models).

Primary outcome analysis

We performed logistic mixed effects regression analyses on characteristics present at the first event to determine associations with the primary outcome, including random intercepts for the individual patient and cohort. We adjusted for the following covariables present at baseline, which were selected based on literature review[7,10,18,19] and clinical plausibility prior to data collection: ICH location, cerebral amyloid angiopathy (present at index ICH), cortical subarachnoid hemorrhage extension (cSAH), hypertension and antihypertensive treatments, including an interaction term for hypertension and antihypertensive treatment to account for potentially uncontrolled hypertension.

To account for collinearity between ICH location, cSAH and CAA, we built two different models – one including ICH location and cSAH, but not CAA and the other one including CAA but not cSAH and location.

Secondary outcome analysis

We performed a mixed effects linear regression, including random intercepts for the individual patient and cohort We determined the association of the following, prespecified covariables with time to recurrence: ICH location, number of previous ICH, any adjacent ICH, hypertension known at previous ICH, anticoagulation on admission for the respective ICH (as a surrogate for anticoagulation pre-treatment, given that medication was not assessed in the interval between two ICH) and sex. Results are reported in as non-standardized coefficients and 95% CI. We plotted the time to recurrence using a Kaplan-Meier curve.

Sensitivity analyses

To further investigate the potentially underlying pathophysiological mechanisms, we restricted our analysis population to patients in whom CAA was diagnosed anytime (at baseline or during follow-up).

Ethical board review

For this project, we collected data from investigator-initiated ICH cohorts. Informed consent and study procedures followed the local regulations at the timepoint of individual patient's inclusion. The primary cohorts and data transfer were approved by a local review board and/or legal entity, if required.

Results

The cohorts consisted of 13429 patients with ICH, of whom we included the 733 patients with at least one recurrent ICH event, resulting in a total of 1616 events (733 index ICH and 883 recurrent ICH, range 1-6 recurrent ICH). 392 patients (53.5%) had at least one MRI during the study period, 538 (73.7%) had at least one CT- or MR-angiography and 95 (13%) underwent digital subtraction angiography. In total, 409 patients (55.8%) were reported to have CAA (33.2% according to the Edinburgh CT-based criteria[6] and 66.8% according to the Boston criteria[16,17], the respective version depended on the timepoint of imaging assessment, including patients who had a diagnosis of CAA prior to their first ICH and did not undergo further MRI). Supplemental table S1 summarizes information about contributing cohorts and supplemental figure S1 displays the study flowchart.

Patient characteristics at index ICH

Mean age at the index ICH was 72.4 years (IQR 65.2-79 years), and 47.2% were female. Of the 733 patients, 393 patients (53.6%) had $_{rem}$ICH and 340 patients (46.4%) had $_{adj}$ICH. Table 1 displays baseline characteristics of all patients and according to the location of recurrent ICH event ($_{rem}$ICH vs $_{adj}$ICH). The total follow-up period was 2.53 years (95% CI 0.66-4.92,) and did not differ between patients who had $_{adj}$ICH (2.69 years, 95% CI 0.61-4.71) versus those with $_{rem}$ICH (2.45, 95% CI 0.68-5.08, p=0.90). During this time, patients with $_{adj}$ICH had more recurrent ICH events (median 1 recurrence, IQR 1-2, range 1-6) than those with $_{rem}$ICH (median 1, IQR 1-2, range 1-4). Patients with $_{adj}$ICH had a higher prevalence of lobar location as index ICH event (261 patients, 79.1% vs. 223 patients, 57.3%, p<0.001) and subarachnoid expansion (120, 42.3% vs 95, 27.5%, p<0.001), while deep index ICH was more frequent in patients with $_{rem}$ICH (27.8% vs. 15.5% Table 1).

Spatial distribution

Information on location of index and recurrent ICH was available in all patients (100%). Of 883 recurrent ICH, 476 occurred adjacent to the index ICH and 407 occurred in remote areas. Figure 1 displays hematoma location at index and recurrent ICH for patients with $_{adj}$ICH compared to those with $_{rem}$ICH. Patients with a lobar index ICH were more likely to have an ICH adjacent to a previous one (53.9% adjacent, 46.1% remote), while those with ICH in deep structures or the cerebellum more often had remote ICH (28.6% adjacent, 71.4% remote, p<0.001). Both, $_{adj}$ICH and $_{rem}$ICH recurred most frequently in the frontal and parietal lobe. On the other hand, frontal, parietal and occipital recurrences were significantly more prevalent in patients with $_{adj}$ICH. While the index ICH seemed to affect the left side more often in patients with $_{adj}$ICH, there was no difference for recurrent ICH. The majority of index ICH was located

in lobar brain areas in CAA patients (86.9%), the index location in patients with non-CAA was lobar in 41.8%, and 42.1% of patients with non-CAA-ICH had a deep supratentorial ICH.

Determinants of adjacent ICH

In the multivariable regression analysis (full model listed in supplemental table S2) including ICH location and cSAH extension (597/733 patients with complete information), we found a positive association of lobar hematoma location (aOR 2.08, 95% CI 1.32-3.27) with $_{adj}$ICH, while cerebellar ICH was inversely associated with $_{adj}$ICH (aOR 0.25, 95% CI 0.07-0.89). In the model including CAA (611/733 patients with complete information), CAA at index ICH was associated with $_{adj}$ICH (aOR 2.21, 95% CI 1.57-3.11). We did not observe an association of hypertension or antihypertensive treatment, even when adjusting for potential interactions (Figure 2).

Time to recurrence

Time to recurrence was available for 873/883 recurrent events (98.9%) and 808 of them were included in the mixed linear regression. For patients with $_{adj}$ICH, the median time to recurrence was 1.25 years (IQR 0.36-3.38). For $_{rem}$ICH, median time to recurrence was 2.21 years (IQR 0.66-4.85). Previous lobar or cortical subarachnoid hemorrhage location (Coef. -0.75, 95%-CI -1.25 to -0.25, p=0.003), $_{adj}$ICH (Coef. -0.60, 95%-CI -1.02 to -0.18, p=0.005) and the number of previous ICH (Coef. 0.62, 95%-CI -0.93 to -0.32, p<0.001, figure 3) were independently associated with a shorter time to recurrence..

Sensitivity analysis restricted to patients with CAA

Information about CAA status was available for at least one time point in 730/733 patients (99.6% supplemental Table S3). Of all included patients, 409 (56.0%) fulfilled the neuroimaging-based Edinburgh or Boston criteria at any time point. Among patients diagnosed with CAA, in 278/409 patients (73.0%), CAA was diagnosed already at the index ICH. Patients with CAA (i.e., on either index or recurrent ICH) were older than those with non-CAA ICH (median age 74 years, IQR 68-80 versus 70 years, IQR 62.8-78).

Spatial distribution

475/538 (88.6%) CAA-associated recurrences occurred in a lobar area, predominantly in the frontal and parietal lobes. In patients with CAA, lobar hematoma location at index ICH (aOR 9.82, 95%-CI 2.80-34.43), but not cSAH was independently associated with suffering a recurrent ICH adjacent to the previous one.

In non-CAA patients, recurrences occurred in deep structures (41.7%), particularly the basal ganglia (91/342 patients, 27.2%) and in lobar areas (37.6%), and cerebellar ICH was associated with a lower odds of $_{adj}$ICH.

Time to recurrence in patients with CAA

In patients with CAA, time to recurrence was significantly shorter (1.23 years, IQR 0.34-3.36) compared to patients without CAA (2.50 years, IQR 0.81-5.11). When restricting the regression model to patients with CAA, the number of previous ICH (Coef -0.49, 95%-CI -0.77 to -0.22)), but not hematoma location or $_{adj}$ICH were associated with a shorter time to recurrence. In patients with non-CAA-ICH, $_{adj}$ICH (Coef. -1.12, 95%-CI -1.94 to -0.29) and the number of previous ICH (Coef. -1.33, 95%-CI -2.42 to -0.24) were associated with a shorter time to recurrence).

Discussion

This large, multi-cohort collaboration analysis including fourteen European cohorts yielded the following main findings: 1) In half of all patients with recurrent ICH, recurrent events occur anatomically adjacent to a previous ICH. 2) The time to recurrence was significantly shorter in patients with $_{adj}$ICH compared to patients with $_{rem}$ICH. 3) CAA was associated with $_{adj}$ICH.

Recurrent ICH is a significant burden for individuals, next-of-kin, carers and hospital personnel. Yet no disease-specific treatment exists that effectively reduces this burden. Therefore, understanding ICH recurrence is a major, yet unmet medical need. Previous studies have identified traditional risk factors for recurrent ICH including uncontrolled hypertension[18], presence of cerebral microbleeds[19], lobar ICH location[20,21] and multifocal cortical superficial siderosis[22]. While this information is suggestive for the most prevalent, pathology associated with recurrent ICH - CAA[7,10,19] –, specific mechanisms leading to recurrence remain poorly understood. Our study goes beyond classical systemic risk factors as we assessed temporal and spatial distribution of ICH recurrence following a tissue-based hypothesis.

The main finding of our study is that we identified a common subgroup of patients that have recurrent ICH events adjacent to the index ICH (approximately 50% of all recurrent ICH), a shorter time-to-recurrence and often had features of CAA. We can only speculate about the reasons that underlie our observation. One potential explanation is that regional disease-related processes – either disease progression[23], significant local disease burden or disease-related inflammation[24,25] – might play a role.

Given the significant association with CAA, pathological processes observed in CAA might play a role, including vessel remodelling[26,27], perivascular compartment related fluid flow disturbance[28], blood-brain-barrier breakdown and related inflammation[29]. However, most observations were made in post-mortem studies of patients deceased after ICH with advanced stages of CAA. Processes in patients with milder forms of CAA or lobar ICH without CAA[6], who survive the index ICH and have the time to suffer a recurrent ICH (like in our study), may differ. Recent observational data reported high frequency of early (within 90 days) ICH recurrence in patients with CAA[30], in line with the findings of our study but the number of patients with recurrent ICH was small in this study. Inflammation and its role in the pathology of CAA-related ICH have gained recent interests[28,31]. Small studies linked post-contrast leakage and enhancement to progression of CAA[32,33] and individual case reports described beneficial effects of immunspression counteracting inflammatory activity in a case of CAA-related recurrent subarachnoid hemorrhage[34]. These reports may point towards vasculopathy-related inflammation as a potential driver of the observations made in our current study.

Two previous small studies[35,36] assessed the spatial and temporal clustering of ICH recurrence but were limited by small sample sizes (both only 24 recurrent ICH) or restricted to patients with CAA and including also asymptomatic hemorrhagic lesions (i.e. cerebral microbleeds)[36]. A recent study assessed spatial and temporal clustering in a sample of 72 patients with hereditary CAA[37] and found that 34% of recurrent ICH occurred in the same lobe as the index ICH, which is in line with our findings. Our study has advantages over those studies through its significant sample size, multi-center setting and the inclusion of all small vessel disease-related ICH providing a more comprehensive picture and allowing us to investigate associations with CAA.

The results of our study do not have immediate clinical implications but suggest the existence of a particularly vulnerable subgroup of patients requiring dedicated prevention of recurrence, who may benefit from novel management options of ICH (e.g. tissue-based treatments). The findings are robust in different sensitivity analyses and models, but should be validated in an unselected ICH cohort including patients with one or more than one ICH. Future studies need to further characterize this patient group including findings from advanced neuroimaging (MRI) studies and histopathology. These studies need to clarify which mechanisms ultimately lead to early and locally adjacent recurrent ICH and whether disease burden, disease progression or inflammation play a critical role.

This study has several limitations: 1) This is a pooled analysis from western European cohorts with different recruitment and follow-up strategies, with a possibility of selection bias. Pooling was done retrospectively. Thus, our findings should be considered as hypothesis-generating. 2) Patients who died were excluded from further follow-up, resulting in a bias towards patients with less severe neurological status. This might lead to an overrepresentation of patients with lobar ICH, who have a better functional outcome[38]. 3) In our analysis, we did not adjust the probabilities of $_{adj}$ICH and $_{rem}$ICH for the relative size of the regions and we did not further differentiate cerebellar ICH location. 4) Neuroimaging assessment was performed by local investigators and not by a central imaging core-lab, and the definition for CAA was based on neuroimaging (either Boston or Edinburgh criteria). For the majority of patients, neither histopathological nor genetic data was available. Thus, patients with smaller CAA-associated hematomas may have been missed when applying the Edinburgh CT-based criteria[39], while CAA diagnosis is no longer possible according to the Boston criteria in patients with deep haemorrhagic manifestations, leading to a potential underrepresentation of patients with mixed CAA-deep perforator arteriolopathy phaenotypes in the CAA-positive group. 5) Patients with a non-CAA pathology may still have heterogeneous underlying diseases. 6) Due to time and

regional differences in guidelines, homogeneous data regarding etiological assessment, classification[7,40] and outcomes throughout the fourteen cohorts was not available.

In conclusion, our study identified a particularly vulnerable subgroup of patients with early recurrent ICH, adjacent to index ICH. This subgroup is significant in size, making up roughly 50% of all patients with recurrent ICH and is significantly associated with CAA and its imaging markers. Our findings offer novel insights into the potential pathophysiological mechanisms of recurrent ICH and suggest a role of tissue-related factors. Based on our findings, we suggest that future studies should further investigate disease activity, including neuroinflammation and neurodegeneration and local disease burden. A deeper understanding may help to identify patients at a particularly high risk for early recurrence and foster the development of new treatments for this population.

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Author Contributions:

Drs Goeldlin and Seiffge had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs Goeldlin and Seiffge

Acquisition, analysis, or interpretation of data: all authors

Drafting of the manuscript: Drs. Goeldlin and Seiffge

Critical revision of the manuscript for important intellectual content: all authors

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Tables and figures:

Table 1: Clinical and neuroimaging characteristics at time of index ICH in patients with recurrent ICH

	Total N = 733	Patients with $_{rem}$ICH recurrence N=393	Patients with $_{adj}$ICH recurrence N=340	p-value
Clinical characteristics				
Age, median (IQR)	72.4 (65.2-79.0)	72 (64-79.0)	72.7 (67.0-79.0)	0.19
Total ICH events, median (IQR)	2 (2-2)	2 (2-2)	2 (2-3)	**<0.001**
Female sex, n (%)	346 (47.2%)	191 (48.6%)	155 (45.6%)	0.42
CAA diagnosed at any timepoint, n (%)	409 (56.0%)	188 (47.8%)	221 (65%)	**<0.001**
CAA present at index ICH, n (%)	278 (43.2%)	119 (33.5%)	159 (55.2%)	**<0.001**
Hypertension, n (%)	450 (66.2%)	242 (65.6%)	208 (66.9%)	0.72
Dyslipidaemia, n (%)	218 (31.6%)	118 (31.6%)	100 (31.7%)	0.96
Diabetes, n (%)	132 (18.9%)	76 (20.1%)	56 (17.5%)	0.38
Atrial fibrillation, n (%)	94 (13.3%)	48 (12.5%)	46 (14.3%)	0.50
Antiplatelet therapy, n (%)	94 (13.3%)	48 (12.5%)	46 (14.3%)	0.50
Anticoagulation, n (%)	83 (11.9%)	48 (12.6%)	35 (11.1%)	0.55
Antihypertensives, n (%)	346 (54.2%)	188 (53.6%)	158 (55.1%)	0.71
Antidiabetics, n (%)	108 (15.7%)	65 (17.4%)	43 (13.8%)	0.20
Lipid-lowering drugs, n (%)	180 (28.3%)	96 (27.5%)	84 (29.4%)	0.60
Systolic blood pressure, median (IQR)	160 (136.5-180)	161.5 (139-180)	154.5 (135-180)	0.078
Diastolic blood pressure, median (IQR)	84 (76-97)	85 (79-99)	81.5 (72-95)	0.061
Neuroimaging characteristics				
Hematoma epicenter at index ICH, n (%)				**<0.001**
Lobar	484 (67.3%)	223 (57.3%)	261 (79.1%)	
Deep	159 (22.1%)	108 (27.8%)	51 (15.5%)	
Brainstem	12 (1.7%)	10 (2.6%)	2 (0.6%)	
Cerebellum	32 (4.5%)	27 (6.9%)	5 (1.5%)	
Isolated IVH	1 (0.1%)	1 (0.3%)	0 (0.0%)	
Isolated cSAH	28 (3.9%)	18 (4.6%)	10 (3.0%)	
Uncertain location	3 (0.4%)	2 (0.5%)	1 (0.3%)	
Side of hematoma at index ICH, n (%)				**0.047**
Right	319 (44.2%)	175 (44.6%)	144 (43.6%)	
Left	385 (53.3%)	202 (51.5%)	183 (55.5%)	
Midline/central	7 (1.0%)	7 (1.8%)	0 (0.0%)	
bilateral	11 (1.5%)	8 (2.0%)	3 (0.9%)	
Intraventricular hemorrhage, n (%)	114 (17.5%)	64 (17.9%)	50 (16.9%)	0.74
Subarachnoid expansion, n (%)	215 (34.1%)	95 (27.5%)	120 (42.3%)	**<0.001**

CAA, cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage;

Figure 1: ICH locations in adjacent vs. remote ICH

Legend: Locations of ICH displayed according to adjICH versus remICH. The left (white-shaded) part displays the distribution of index ICH locations, the right (grey-shaded) part displays the distribution of ICH recurrences.

Figure 2: Odds ratio for adjacent ICH vs remote recurrent ICH (reference) using two different models

Legend: Coefficient plot displaying the odds ratios for all covariables included in the two models for the primary outcome, including the interaction term for hypertension and antihypertensives (Hypertension#Antihypertensives). CAA, cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage.

Figure 3: Associations with time to recurrence

Legend: Association of covariables with the time to recurrence (event-based analysis).

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