Proportion of intracerebral haemorrhage due to cerebral amyloid angiopathy in the East and West: comparison between single hospital centres in Japan and the United Kingdom

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Word count: abstract, 235; text, 3776

Itemized list: Tables, 3; Figure, 2, References 31

Supplementary material: Supplemental Methods and References, Tables (S1-S7), and Figure S1.

Abstract

Purpose: We investigated whether the proportion of intracerebral haemorrhage (ICH) due to cerebral amyloid angiopathy (CAA) differs between patients admitted to hospitals in the East and the West.

Methods: This international cross-sectional study included consecutive spontaneous ICH patients admitted to one stroke centre in the United Kingdom (Western centre origin) and one in Japan (Eastern centre origin) during the same period. We classified spontaneous ICH into "CAA-related" or "other" using the Edinburgh CT-based diagnostic criteria. We used multivariable logistic regression analyses to assess the relationship between CAA-related ICH and geographical location or ethnicity (East Asian vs. other). Sensitivity analyses were performed using the modified Boston MRI-based diagnostic criteria for CAA-related ICH.

Results: Of 433 patients (median age, 72 years; Western centre origin, 55%), 15% were classified as CAA-related ICH. In the multivariable logistic regression model, Eastern centre and ethnicity had a lower proportion of CAA-related ICH (odds ratio [OR] vs Western centre origin 0.55, 95%CI 0.31-0.98; OR [vs. White] 0.47, 95%CI 0.25-0.87); these findings remained robust in sensitivity analyses. The estimated incidence of "other" (non-CAA) ICH (attributed to hypertensive arteriopathy) was 2.5-fold higher in East Asian populations.

Conclusions: The proportion CAA-related ICH is lower in an Eastern compared to a Western hospital ICH population; this might be explained by a higher incidence of ICH related to hypertensive arteriopathy in East Asian populations, suggesting that optimal ICH prevention strategies might differ between the East and West.

Keywords: cerebral small vessel disease; intracerebral haemorrhage; ethnicity; cerebral amyloid angiopathy; hypertension; cerebral microbleeds

1. Introduction

Sporadic cerebral amyloid angiopathy (CAA), characterized by the progressive deposition of amyloid-β protein in the small- to medium-sized vessel walls in the cerebral cortex and overlying leptomeninges, is a common age-related cerebral small vessel disease (SVD) in the elderly [1, 2], (especially those with Alzheimer's disease [3, 4]). CAA is most often recognized clinically by symptomatic intracerebral haemorrhage (ICH) restricted to the lobar areas of the brain, by contrast with hypertensive arteriopathy (also termed deep perforator arteriopathy or arteriolosclerosis) which is associated with ICH in both deep and lobar brain regions [5]. Given the aging of populations globally, CAA is an increasing public health challenge [5]. Effective treatment and prevention for CAA and its associated phenotypes (including ICH) requires a better understanding of the mechanisms and underlying spectrum of SVD.

Differences in genetic or environmental exposures in different geographical regions appear to influence the prevalence and spectrum of small vessel diseases that cause most spontaneous ICH. First, the incidence of ICH is twice as high in Eastern compared to Western populations [6]. Second, autopsy studies suggest that the proportion of lobar ICH attributed to CAA is lower in Eastern populations (e.g. 20-31% in Japan [7-9]) than in Western populations (e.g. 74% in the United States [10]). Third, the age-specific prevalence of CAA in autopsy series from Eastern populations is lower than in Western populations [11]. However, little is known about whether the proportion of ICH due to CAA differs between Eastern and Western clinical hospital cohorts.

We therefore aimed to investigate whether geographical location, ethnicity, or both, are associated with the proportion of ICH attributed to CAA in one hospital centre in London

and one in Japan. We hypothesized that the proportion of CAA-related ICH is lower in the East than in the West.

2. Methods

The study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline [12]. The study received ethical approval by Clinical Lead for Information Governance at the National Hospital for Neurology and Neurosurgery as part of a registered service evaluation (no specific approval number) and by Saga University Faculty of Medicine (approval number 27-45). Because cohorts shared only anonymized data, individual consent was not required. Y.Y. and D.J.W had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Our dataset can be shared on request after appropriate approval by the participating hospitals.

2.1. Patients

We included consecutive patients diagnosed with spontaneous ICH at two specialist hospital stroke centres over the same time period: London, United Kingdom (UK); and Saga, Japan. Cases were systematically ascertained using multiple overlapping methods from prospective clinical databases and radiological reports. UK patients were identified from a database of University College London Hospitals National Health Service Foundation Trust, London, UK, and were classified as "Western centre origin"; Japanese patients were collected from a database of Saga University Hospital, Saga, Japan and were classified as "Eastern centre origin." To be included in this study, subjects had to meet the following criteria: (1) age ≥20 years; (2) acute ICH; and (3) admitted to one of

the specialist stroke centres between December 2010 and May 2013. Patients in whom the timing of onset was not clear were also included if a typical acute ICH was identified on their brain computed tomography (CT) by either a certified stroke specialist (Y.Y.) or a certified neuroradiologist (T.N.). Exclusion criteria were: (1) secondary ICH associated with haemorrhagic transformation of an infarct, arteriovenous malformation or fistula, cavernous malformation, subarachnoid haemorrhage due to raptured aneurysm, hematologic disease, vasculitis, tumour, traumatic, iatrogenic, or coagulation abnormality (prothrombin time international normalizing ratio (PT-INR)>4.0 on warfarin); (2) incomplete CT data; or (3) haematoma involving the majority of a hemisphere which could not be categorized as lobar or non-lobar to allow CAA classification (please see the "Imaging analyses" section).

2.2. Baseline assessments

Clinical and demographic findings (including age, sex, and ethnicity) were obtained from medical records review using a standardized data collection form. The use of antithrombotic drug(s) was recorded and the PT-INR was obtained from patients treated with warfarin. Definitions of other clinical variables (current smoking status, presence of hypertension, diabetes mellitus, and dyslipidaemia) are described in supplemental material (Supplemental Methods).

2.3. Imaging data collection

All patients were evaluated by brain CT on admission. Further investigation with magnetic resonance imaging (MRI), including blood-sensitive MRI sequence(s) (gradient-echo T2*-weighted imaging sequence, susceptibility-weighted imaging [SWI],

or both, performed within a year after ICH onset) were performed as part of standard clinical care at the discretion of the attending physicians. If a patient had both types of blood-sensitive MRI imaging, the SWI was used for the analysis. We recorded days from ICH to MRI, magnetic field strength, sequence type, and echo times. The details of the MRI protocol in each centre are shown in online supplement (Table S1).

2.4. Imaging analyses

2.4.1. Definition of haemorrhagic findings

Acute spontaneous ICH was defined as a symptomatic stroke syndrome associated with imaging evidence of ICH without evidence for an underlying cause, except for sporadic SVD. Hematoma location was defined according to the Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS) as "lobar" or "other" [13]. If hematoma involved the majority of a hemisphere (e.g. the ICH was too large [>50ml] and extended into both lobar and non-lobar areas), the location was classified as "uncertain" and the patient was excluded from the analysis. ICH located in both lobar and non-lobar areas were classified as "mixed".

The presence of the following two putative markers of CAA on CT, as defined in the Edinburgh CT diagnostic criteria [14], were ascertained: a) subarachnoid haemorrhage (SAH), which also called "acute convexity SAH [15]", defined as extension of the haemorrhage into the extra-axial subarachnoid space; and b) finger-like projections (FLPs), defined as elongated extension(s) arising from the hematoma, longer than they are wide, regardless whether they extend to the cortex or not.

Definition and classification of haemorrhagic findings on blood-sensitive MRI (cerebral microbleeds [CMBs] and cortical superficial siderosis [cSS]) were performed

according to recent consensus criteria or validated scales [16-19] as described in supplemental material (Supplemental Methods).

2.4.2. Rating of haemorrhagic findings

ICH, CMBs and cSS, were analysed by a clinical neurologist (D.W.) blinded to our hypothesis and to all clinical information. Inter-rater reliability testing was performed with 50 randomly selected scans rated by 2 clinical neurologists (D.W. and Y.Y.), and intra-rater reliability was determined from 20 randomly selected scans scored twice by each observer. These reliabilities were evaluated for ICH and CMBs by each location (lobar, deep, and infratentorial), as well as any cSS, and expressed as Cohen's κ value.

SAH and FLPs in patients with lobar ICH were analysed by a clinical neurologist (J.B) blinded to our hypothesis and to all clinical information. Inter-rater reliability testing was performed with 20 randomly selected scans rated by 2 raters (J.B. and M.N.) who were trained using the Edinburgh Criteria for CAA-associated ICH Training on the website (https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/education-teaching/short-courses/training-tools/edinburgh-criteria-for-caa-associated-ich-training). The intra-rater reliabilities for SAH and FLPs were determined from 20 randomly selected scans scored twice by each observer. All haematoma volumes were manually measured by the formula ABC/2 [20] by a single rater (Y.Y.).

2.4.3 Definition of CAA-related ICH

Strictly lobar ICH was defined as haematoma restricted to lobar area(s) (including the cerebellum) [10]. According to the Edinburgh CT diagnostic criteria [10], the probability of CAA-related ICH classified as: not CAA (patients with non-lobar ICH); low (patients with strictly lobar ICH, but neither SAH nor FLPs); medium (patients with strictly lobar ICH and SAH *or* FLPs); or high (patients with strictly lobar ICH with both SAH *and* FLPs). CAA-related ICH was defined as a medium or high probability of CAA. Originally, the CT-based Edinburgh criteria for CAA-related ICH in patients with (strictly) lobar ICH used 3 variables including SAH, FLPs, and apolipoprotein E4 [14]. However, since it is difficult to obtain the data of apolipoprotein E genotyping in clinical practice, a simplified model on the basis of CT features alone was also assessed: sensitivity (95% confidence interval [CI], and specificity (95%CI) for having SAH only, 0.89 (0.73-0.96) and 0.58 (0.37-0.76), respectively; those for having SAH and FLPs, 0.39 (0.24-0.56) and 1.00 (0.84-1.00), respectively. Regarding cases with FLPs only, there was no data for the diagnostic test accuracies in that study [14], but FLPs was found in cases of lobar ICH with moderate or severe CAA, making them very specific for CAA-associated ICH. This allowed us to define of "patients with FLPs only" as CAA-associated ICH.

For the sensitivity analysis, in which patients evaluated by both brain CT and MRI were included, the CAA-related ICH group was defined as multiple haemorrhagic lesions (ICH, CMBs, or both) restricted to lobar areas (including the cerebellum) or a single haemorrhagic lesion restricted to a lobar area with any additional cSS in patients aged 55 or older (i.e. “probable CAA” according to the modified Boston criteria [19]).

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 21.0 (IBM, Armonk, NY, USA). Univariate analyses were performed to compare variables between groups, using the Mann-Whitney *U* test or chi-square test, as appropriate. For the primary analysis (using the CT-based cohort), multivariable binary logistic regression analyses were applied to estimate adjusted odds ratios (OR) and 95%CI of CAA-related ICH according to geographical location as follows: model 1 (unadjusted); model 2 (adjusted for age and sex); model 3 (further adjusted for hypertension, antithrombotic use and previous stroke based on their potential associations with spontaneous ICH subtype). Model 2 was our primary analysis as there was no missing data for confounders (age and sex). Model 3 was considered a secondary analysis because information on additional confounders was not available for all patients. We also examined whether there was an independent association between ethnicity (White vs. East Asian or other ethnicities) and CAA-related ICH in a similar manner.

We did sensitivity analyses in patients with both CT and MRI data with the final models adjusted for age, sex, hypertension, previous stroke, antithrombotic use, 3T field strength, and echo time. The association between patients with CAA-related ICH by Edinburgh CT diagnostic criteria and those by modified Boston criteria was also evaluated by chi-square test and multivariable binary logistic regression analysis. Values of $p < 0.05$ were considered statistically significant.

Based on the published incidence of ICH (per 100,000 year-person) in white (24.2, 95% confidence interval [CI] 20.9-28.0) or East Asian populations (51.8, 95%CI 38.8-69.3) in a previous meta-analysis [6], and the proportion of CAA-related ICH in each ethnicity type by CT-based classification, we estimated the incidences for CAA-related ICH for each ethnicity group using the following formula:

Estimated incidence of CAA-related ICH = the proportion of CAA-related ICH × published incidence of all ICH in each ethnicity (per 100,000 person-year)

We calculated the estimated incidence of "other" ICH in the same way. We did sensitivity analyses of these estimations using the CT and MRI-based classifications of CAA.

3. Results

Fig. 1 shows the patient flow diagram: the full CT-based cohort included 433 patients with spontaneous ICH (median age, 72 years; 54% male), of whom 40 (9%) had surgical intervention. Among them, 240 patients of Western centre origin included 144 whites, 4 East Asians, and 70 other ethnicities (ethnicity data was not available from 22 patients). All 194 patients of Eastern centre origin were East Asian (Table S2).

The inter-rater and intra-rater reliabilities for haemorrhagic findings are described in Table S3. Briefly, they ranged from 0.65 to 0.94 and from 0.63 to 1.00, suggesting moderate to excellent reliability. The results of those for the specific CT findings of the Edinburgh CT diagnostic criteria were as follows: SAH, 0.80 and 0.69-0.90; FLPs, 0.78, 0.63-0.88. Most of the patients (96.5%) had a single haematoma; 3.5% had multiple haematomas (multiple lobar [2.1%], multiple other [0.7%], and mixed [0.7%]).

In the univariate comparisons of clinical characteristics between the centres (Table 1), patients of Eastern centre origin had: a higher proportion of current smokers and patients

with previous stroke; and a lower prevalence of antithrombotic drug(s) use, dyslipidaemia, strictly lobar ICH, and SAH. Patients with a medium or high probability of CAA-ICH were more common in Western compared to Eastern centre origin.

3.1. Primary analysis

There were 65 patients with CAA-related ICH (15%) and 368 with other ICH (85%). Compared to other ICH, CAA-related ICH patients were older, less often of male or of Eastern centre origin, with a lower prevalence of hypertension (Table 2). Table 3 shows the results of the main analyses of the proportion of ICH attributed to CAA according to geographical location. Our primary model (Model 2) revealed that patients of Eastern centre origin had a lower odds of CAA-related ICH (OR 0.55, 95%CI 0.31-0.98). Model 3 (including 90% of the total cohort) also showed a similar association. Patients of East Asian ethnicity also had a lower odds of CAA-related ICH than those of White ethnicity in all of the models (Table 3).

3.2. Estimated incidence of each type of spontaneous ICH

Using our observed proportions of CAA-related ICH (23.8% in patients of White ethnicity; 10.2% in patients of East Asian ethnicity in the full CT-based cohort), the estimated incidences (per 100,000 person-year [95%CI]) for CAA-related ICH and other ICH were calculated (Fig. 2). The incidence of CAA-related ICH in patients of East Asian ethnicity (5.3 [4.0-7.1]) was similar to that in those of White ethnicity (5.8 [5.0-6.7]), but

the rate of other ICH was 2.5-fold higher in those of East Asian ethnicity (46.5 [34.8-62.2]) compared to those of White ethnicity (18.4 [15.9-21.4]).

3.3. Sensitivity analyses

The sensitivity and specificity of Edinburgh CT diagnostic criteria for CAA-related ICH defined by modified Boston criteria were 0.62 and 0.94, respectively. A logistic regression analysis (adjusted for age and sex) revealed that CAA-related ICH defined by Edinburgh CT diagnostic criteria was associated with a higher odds of CAA defined by the modified Boston criteria (OR 20.23, 95%CI 7.60-53.85). The characteristics of the CT and MRI cohort are shown in Tables S4 and S5. The proportion (%) of patients performed MRI scan after 30 days after ICH onset was lower in participants of Eastern compared to Western centre origin (7% vs. 23%, respectively, p=0.001, chi-square test), while, there was no difference in the duration (days) from admission to MRI between two centres (Western vs. Eastern, median [interquartile range]: 9 [4-27] vs. 9 [6-13], *p*=0.412, Mann-Whitney *U* test). The results of univariate analysis of differences in patient characteristics according to CAA status (Table S6) were consistent with the results of the primary analysis. The results of multivariable logistic regression analysis of factors associated with CAA-related ICH defined using the MRI-based Boston criteria (Table S7) also confirmed the primary analysis: model Ⅱ (adjusted for age and sex; no missing data) revealed that patients of Eastern centre origin had a lower odds of CAA-related ICH (OR 0.22, 95%CI 0.09-0.53) compared to those of Western centre origin; model Ⅴ (adjusted for age and sex; no missing data) showed that patients of East Asian ethnicity had a lower odds of CAA-related ICH (OR 0.19, 95%CI 0.08-0.49). These associations

were robust even when further adjusted for previous stroke, antithrombotic use, hypertension, 3T use, and echo time (models Ⅲ and Ⅵ). In analyses further adjusted for the patients with MRI scan performed beyond 30 days from ICH onset, similar associations were found (data not shown). The estimated incidences for each ICH type (Fig. S1) were also similar to the results of the full CT-based cohort.

4. Discussion

The major finding of our study is that CAA accounts for a higher proportion of spontaneous ICH in a Western hospital centre (London UK) than in an Eastern hospital centre (Saga, Japan). Our findings in sub-analyses suggest that White ethnicity, rather than environmental factors, is the main factor explaining the relationship of geographical location to the proportion of ICH attributed to CAA. These associations were robust after adjustment for potential confounding factors, and regardless of whether CT- or MRI-based criteria were used to diagnose CAA.

A systematic review of autopsy series hypothesized that there are ethno-racial or geographical differences in the proportion of ICH related to CAA and in the age-specific prevalence of CAA[11]; CAA accounted for a smaller proportion of ICH and was less common at all ages in Eastern compared to Western cohorts. However, few clinical studies have investigated the spectrum of ICH using brain imaging to determine the underlying causal small vessel disease. The Northern Manhattan prospective population-based epidemiologic study, showed that the incidence of lobar ICH was higher in those of African-American ethnicity than in those of white ethnicity [21]. However, lobar ICH

is not specific for a single type of arteriopathy, and can be due to both CAA or hypertensive arteriopathy (i.e deep perforator arteriopathy or arteriolosclerosis) [14]. Thus, to the best of our knowledge, the data we present is the first to compare the proportion of ICH due to CAA using validated diagnostic criteria across different geographical locations and ethnicities.

Our estimated incidences for CAA-ICH (similar between White and East Asian populations) and "other" ICH likely due to hypertensive arteriopathy (2.5-fold higher in the East Asian compared to White population) support the hypothesis - suggested in a review of autopsy studies - that the lower proportion of CAA-related ICH in the Eastern countries compared to the Western countries probably reflects a higher incidence of ICH related to hypertensive arteriopathy rather than a lower incidence of CAA-related ICH [11].

This clear difference in the proportion of ICH presumed due to hypertensive arteriopathy [22]) between East and West is not accounted for by a statistically significant difference in the prevalence of hypertension between our hospital-based cohorts. One possible explanation is that there is a difference in the susceptibility to hypertension as a result of genetic factors associated with ethnicity, climate, or latitude [23]. Consistent with our findings, a recent international collaborative meta-analysis in healthy populations found that Eastern populations had a higher prevalence and number of "hypertensive" CMBs but a similar prevalence and number of strictly lobar CMBs (a putative marker of CAA), compared to Western populations [24]. Taken together with previous autopsy and pathological studies [7-11]) and our current findings, the available data are consistent with the hypothesis that deep cerebral small vessels are more vulnerable to the effects of

chronic hypertension in Eastern than in Western populations, leading to an increased tendency for micro- and macro-haemorrhage. Possible causes of such vulnerability could include either susceptibility differences in endothelial cells of cerebral small vessels to hypertension [25], the prevalence or effect of the apolipoprotein E genotype [24, 26], or both. Another possibility is that there is bias, caused by the method of ICH aetiology diagnosis, or the treatment or severity of hypertension (quantifiable by duration, number of antihypertensive drugs, or blood pressure values), influencing the estimated prevalence of hypertension and thus the proportion of "other" ICH in the East and West. Finally, a possible direct effect of salt intake on the vascular endothelium (independent of blood pressure) should be considered [27]. Estimated daily salt intake is higher in Asian Pacific (mean 12.71 g/day) high income countries compared to those in Western Europe (mean 8.75g/day) [28]. Moreover, several studies reported that daily salt intake was independently associated with white matter lesions even after adjustment for hypertension [27, 29].

Our study has several strengths. First, we included consecutive spontaneous ICH patients referred to specialist stroke centres over the same period, reducing the confounding effects of secular treatment trends. Second, we included patients with acute surgical intervention, allowing us to evaluate all spontaneous ICH patients referred to the stroke centres, and avoid selection bias. Third, we systematically evaluated brain images using validated criteria and scales by trained raters, blinded to our hypothesis. Finally, our selection of representative developed (high-income) countries in the East (Japan) and West (UK) decreased the potential for socioeconomic bias in ICH spectrum and incidence [30].

We also acknowledge limitations. First, the relatively small sample size, comprising patients in single hospital centres in the UK and Japan, limits our statistical power, and the generalizability of our findings to the entire populations of Eastern or Western countries. In particular it is possible that the proportion of ICH attributed to CAA does not reflect the wider populations (e.g., because CAA-related ICH patients are older, they might be less likely to be transferred to a specialist stroke centre, but treated in general hospitals instead). To confirm these findings, further investigation with international collaborative networks would be helpful to increase the scale of data available, maximize statistical power, and increase generalizability [31]. Second, its retrospective design should be considered as a source of bias, although both stroke centres consistently and prospectively collected data in stroke registries. Third, the effect of high early lethality of ICH may differ by ethnicity, country, and hospital, so there might be an unmeasured difference in the number of undiagnosed ICH patients who died prior to CT between the stroke centres. Fourth, different indications for MRI in ICH patients between the hospitals might have affected our sensitivity analyses. Fifth, we did not have pathological confirmation of CAA, although the Edinburgh CT diagnostic criteria and the modified Boston criteria have been reported to have good diagnostic accuracy. Sixth, apolipoprotein E genotype was not available, but could increase the diagnostic accuracy for CAA-ICH when using acute CT [10].

5. Conclusions

Our study demonstrates that the proportion of ICH due to CAA is lower in an Eastern hospital centre (Japan) compared to a similar specialist hospital centre in the West

(London, UK). This difference appears to be explained by a higher incidence of ICH attributed to hypertensive arteriopathy in the Eastern centre, which might reflect an increased vulnerability to the effects of hypertension on deep cerebral small vessels. Our findings suggest that optimal ICH prevention strategies might differ between Eastern and Western populations.

Authors' contributions

YY- study design, data collection, imaging analysis, statistical analysis, interpretation of data, drafting/revising of the manuscript; JT- major role in data collection, revising of the manuscript; DW- major role for imaging analysis, interpretation of data, revising of the manuscript; AC- study design, data collection; TN- data collection, imaging analysis; MN and JB- imaging analysis; MK, TI, YN, MM, HH- data collection, data interpretation; DJW- study design, interpretation of data, drafting/revising of the manuscript.

Funding

This work was supported by a Grant-in-Aid for Scientific Research (C), JSPS KAKENHI (Grant Number 15k10364). This work was also partly undertaken at UCLH/UCL which receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme.

Disclosures

None

Conflict of interest

None

Acknowledgements

We wish to thank Ms. Ikue Tanaka and Ms. Yoshiko Katsuki for acquiring clinical data, and inputting data.

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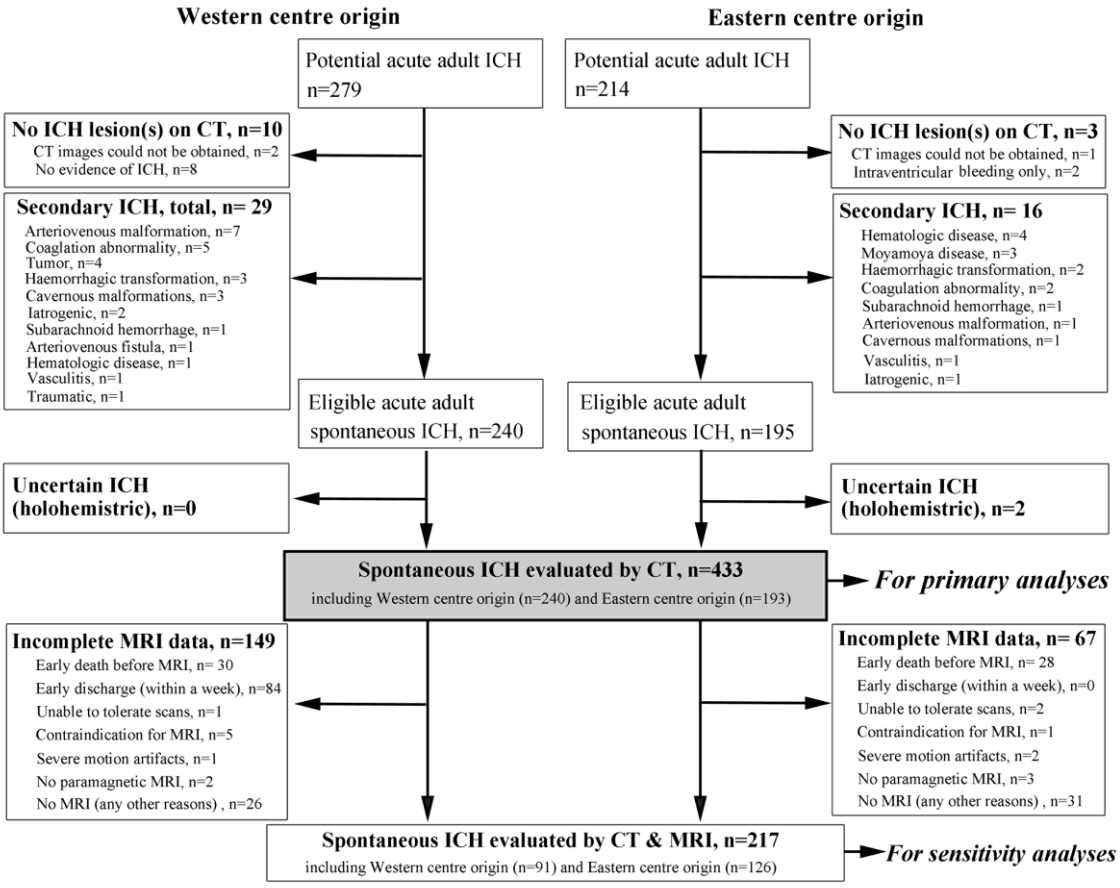
Figures and figure legends

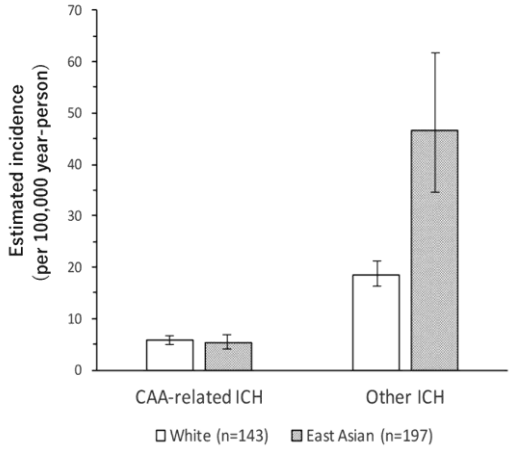
Fig. 1. Flow diagram of patient selection.



Of 493 consecutive patients considered, 433 spontaneous ICH patients with CT (CT-based cohort) are included for primary analyses. Of those, 217 patients furtherly evaluated with blood-sensitive MRI (CT/MRI-based cohort) are used for sensitivity analyses.

Abbreviations: CT: computed tomography; ICH: intracerebral haemorrhage; MRI: magnetic resonance imaging

Fig. 2. Estimated incidence and its 95%CI of each type of ICH by White and East Asian ethnicity.



Abbreviations: CAA: cerebral amyloid angiopathy; CI: confidence interval; ICH: intracerebral haemorrhage

White represents estimated incidence of each type of ICH (per 100,000 person-year) in White ethnicity. Grey represents that in East Asian ethnicity.

The error bars indicated 95% CI.

Table 1. Comparisons of clinical characteristics between Eastern and Western centre origin.

Variables	Western centre origin n=240 (55%)	Eastern centre origin n= 193 (45%)	p Value
On-set to Admission, days [a]	0 (0-0)	0 (0-0)	0.148
Age, years	73 (59-83)	71 (61-80)	0.203
Sex, male	124 (52)	109 (56)	0.318
Current smoker	21 (10)	36 (21)	0.004
Previous stroke	20 (10)	47 (25)	<0.001
Antithrombotic drug(s) use	78 (38)	42 (23)	0.001
Hypertension	148 (69)	140 (74)	0.268
Diabetes mellitus	32 (15)	35 (19)	0.378
Dyslipidaemia	74 (35)	28 (15)	<0.001
Haematoma volume, ml	10.1 (3.1-28.4)	10.6 (4.6-24.8)	0.400
Strictly lobar ICH	88 (37)	39 (20)	<0.001
Subarachnoid haemorrhage	39 (16)	16 (82)	0.013
Finger-like projections	23 (10)	12 (6)	0.202
Probability of CAA-ICH*			0.001
Not CAA	152 (63)	154 (80)	
Low	43 (18)	19 (10)	
Medium - High	45 (19)	20 (10)	

Data presented as median (interquartile range) for continuous variables and number (percentages) for categorical variables.

* According to the Edinburgh CT diagnostic criteria [14], the probability of CAA-related ICH is divided into 4 categories: not CAA (patients with non-lobar ICH); low (with strictly lobar ICH, but neither SAH nor FLPs); medium (with strictly lobar ICH and SAH or FLPs); or high (with strictly lobar ICH with both SAH and FLPs). CAA-related ICH was defined as a medium or high probability of CAA-ICH.

Abbreviations: CAA= cerebral amyloid angiopathy; ICH: intracerebral haemorrhage

All data was <10% missing except for smoking (11.1%).

Table 2. Differences in patient characteristics according to CAA status

Variables	Other ICH *n*=368 (85%)	CAA-related ICH n= 65 (15%)	p Value
Age, years	70 (59-80)	80 (71-86)	<0.001
Sex, male	211 (57)	22 (34)	<0.001
Eastern centre origin	173 (47)	20 (31)	0.015
Current smoker	50 (15)	7 (12)	0.456
Previous stroke	56 (17)	11 (18)	0.771
Antithrombotic drug(s) use	104 (31)	16 (28)	0.607
Hypertension	257 (76)	31 (51)	<0.001
Diabetes mellitus	56 (17)	11 (18)	0.809
Dyslipidaemia	86 (26)	16 (26)	0.907

Data presented as median (interquartile range) for continuous variables and number (percentages) for categorical variables.

Abbreviations: CAA: cerebral amyloid angiopathy; ICH: intracerebral haemorrhage;

All data was <10% missing except for smoking (11.1%).

Table 3. Multivariable logistic regression analyses of associations of geographical location and ethnicity with CAA-related ICH.

Geographical location	Model 1	Model 2	Model 3
Eastern centre origin	0.50 (0.29-0.88)	0.55 (0.31-0.98)	0.48 (0.25-0.93)
Ethnicity	Model 4	Model 5	Model 6
East Asian	0.37 (0.20-0.67)	0.47 (0.25-0.87)	0.41 (0.20-0.84)
Other ethnicities	0.42 (0.18-0.96)	0.59 (0.25-1.39)	0.63 (0.24-1.66)

Odds ratios (95% confidence intervals) for CAA-related ICH according to geographical location (Eastern vs. Western centre origin [Reference]) are presented in models 1, 2 and 3. Odds ratios (95% confidence intervals) for CAA-related ICH according to ethnicity (East Asian and other ethnicities vs. White [Reference])

Abbreviations: CAA: cerebral amyloid angiopathy; ICH: intracerebral haemorrhage

Model 1: unadjusted; included all patients (n=433); Model 2: adjusted for age, sex; included all patients; Model 3: further adjusted for previous stroke, antithrombotic use, and hypertension (n=389); Model 4: unadjusted; included 411 patients with ethnicity data; Model 5: adjusted for age, sex (n=411); Model 6: further adjusted for previous stroke, antithrombotic use, and hypertension (n=370).