Samarasekera N, Fonville A, Lerpiniere C, Farrall AJ, Wardlaw JM, White PM, Smith C, Salman RA, Lothian Audit Treatment Cerebral. Influence of Intracerebral Hemorrhage Location on Incidence, Characteristics, and Outcome Population-Based Study. *Stroke* 2015, 46(2), 361-368.

Title

The influence of intracerebral haemorrhage location on incidence, characteristics and outcome: a population-based study

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Subject codes: Intracerebral haemorrhage

Key words: Intracerebral haemorrhage, prognosis, incidence

Word count: 6271, 250 abstract

Abstract

Background: The characteristics of intracerebral haemorrhage (ICH) may vary by ICH location because of differences in the distribution of underlying cerebral small vessel diseases. Therefore, we investigated the incidence, characteristics and outcome of lobar and non-lobar ICH.

Methods: In a population-based, prospective inception cohort study of ICH, we used multiple overlapping sources of case ascertainment and follow-up to identify and validate 166 ICH diagnoses in 2010-2011 in an adult population of 695,335.

Results: The overall incidence of lobar ICH was similar to non-lobar ICH (9.8 [95% confidence interval (CI) 7.7-12.4] versus 8.6 [95%CI 6.7-11.1] per 100,000 adults per year). At baseline, adults with lobar ICH were more likely to have preceding dementia (21% vs. 5%, p=0.01), lower Glasgow Coma Scale scores (median 13 vs. 14, p=0.03), larger ICHs (median 38ml vs. 11ml, p<0.001), subarachnoid extension (57% vs. 5%, p<0.001), and subdural extension (15% vs. 3%, p=0.02) than those with non-lobar ICH. One year case fatality was lower after lobar ICH than after non-lobar ICH (adjusted OR for death at one year: lobar vs. non-lobar ICH 0.21, 95% CI 0.07 to 0.63; p=0.006, after adjustment for known predictors of outcome). There were four recurrent ICHs, which occurred exclusively in survivors of lobar ICH (annual risk of recurrent ICH after lobar ICH 11.8%, 95% CI 4.6% to 28.5% vs. 0% after non-lobar ICH; log-rank p=0.04).

Conclusion: The baseline characteristics and outcome of lobar ICH differ from other locations.

Introduction

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) accounts for ~10% of all strokes in Western populations.[1] Roughly four-fifths of ICHs with no apparent cause (so-called 'primary' ICH[2]) are usually attributed to small vessel vasculopathies such as arteriolosclerosis or cerebral amyloid angiopathy (CAA). This attribution is usually made on the basis of risk factors, clinical and radiographic features,[3] such as those described by the modified Boston criteria for 'CAA-related' ICH.[4,5]

The incidence of lobar primary ICH appears to be increasing,[1,6] possibly due to antithrombotic drugs.[7] One year case fatality after primary ICH is ~55%,[1] but it is higher after infratentorial ICH.[8,9] However, most ICHs are supratentorial and the influence of supratentorial ICH location on outcome remains unclear. Lobar ICH may have a better prognosis in comparison to ICH in other locations,[10-13] or it may not,[14-20] and the risk of recurrence may be higher after lobar ICH.[21]

Determining whether risk factors and outcome differ according to ICH location has been further complicated by studies' varied definitions of ICH location. Of 41 observational studies comparing lobar and non-lobar ICH, 20 did not define lobar location,[18,22-40] and 21 used different definitions of lobar location (including ICH which was cortical and/or subcortical,[41-46] cerebellar,[47] predominantly cortical and/or involving underlying white matter,[48-50] subcortical or in a hemisphere excluding the basal ganglia or thalamus,[51-53] or in any lobe(s) of the brain[54-61]). Of 28 studies which defined 'non-lobar' ICH, 20 defined 'non-lobar' as involving the basal ganglia or infratentorial regions,[18,25,27,32,33,36,38,45-47,50-54,56-60] seven

included deep periventricular white matter,[41-44,48,49,61] and one included 'subcortical' structures.[55]

Therefore, we sought to define and categorise lobar and non-lobar ICH in a prospective, population-based cohort study in order to determine ICH incidence and its outcome by location, and investigate whether any differences are explained by baseline characteristics.

Methods

Community-based inception cohort study of ICH

The Lothian Audit of the Treatment of Cerebral Hemorrhage (LATCH) ascertained all residents in the Lothian Health board region of Scotland (mid-2010 population aged ≥16 years was 695,335) who were aged ≥16 years at the time they were diagnosed with first-ever or recurrent ICH confirmed by brain imaging or pathology between 1st June 2010 and 31st May 2011 inclusive. We excluded adults with exclusively extra-axial intracranial haemorrhage or ICH definitely attributable to trauma or hemorrhagic transformation of an ischaemic stroke.

We identified incident ICH cases using multiple overlapping sources of case ascertainment. Prospective 'hot pursuit' sources included a collaborative Lothian-wide network of physicians, neurologists, neurosurgeons, radiologists, pathologists, stroke specialist nurses and stroke audit personnel, daily multidisciplinary neuroradiology meetings and a daily review of all CT head scans. We retrospectively reviewed the electronic patient records system in secondary care, records of sudden deaths held by the Office of the Procurator Fiscal, the Scottish Stroke Care Audit [www.strokeaudit.scot.nhs.uk], and ICD-10-coded central records of hospital

discharges held by the Information Services Division [www.isdscotland.org]) for cases missed by hot pursuit.

Definition of lobar and non-lobar ICH

We defined ICH as a symptomatic event (new headache, altered level of consciousness or neurological symptoms), with or without new neurological signs, referable to a focal collection of blood within the brain parenchyma (seen on brain imaging or at autopsy), with signal characteristics on brain imaging or organisation of the haematoma at autopsy consistent with the time of symptom onset, which was not attributable to prior trauma or haemorrhagic transformation of an ischaemic stroke or an alternative explanation.

At least one experienced consultant neuroradiologist (with a special interest in stroke and greater than 10 years neuroradiological practice) reviewed diagnostic brain imaging and classified ICH location as 'non-lobar' if an adult had a single infratentorial ICH (located in the brainstem or cerebellum), a single supratentorial deep ICH (located in the basal ganglia, internal or external capsule or thalamus without extension to a lobar area), or multiple ICHs in solely non-lobar locations (either supratentorial deep or infratentorial). All other ICHs were 'lobar'.

Clinical information

We collected clinical variables by interviewing patients or their families at the time of presentation and reviewing primary care and hospital records. We used two different definitions of hypertension. Firstly, we classified an adult as having a past history of hypertension if either a history of hypertension had been documented in their medical records or if they were taking antihypertensive medications at the time of their ICH. Secondly, we compared the proportion of participants taking antihypertensive

medications between the two groups as a surrogate marker of how well hypertension was controlled in the two groups. We classified an adult as having a past history of dementia either if dementia had been diagnosed prior to the ICH or if a relative or close friend completed the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the score was ≥64.[62]

We used multiple sources of follow-up including those used for case ascertainment, death certificates and questionnaires sent annually to each adult's GP to determine vital status at one year, dependence according to the modified Rankin scale,[63] and the occurrence of recurrent ICH in the first year following their ICH.

Regulatory approval

LATCH was approved by the NHS Lothian Caldicott Guardian. Patients in NHS Lothian were informed about the use of their data for audit, and information leaflets about LATCH were distributed to inform patients and their carers about their right to opt out. Analyses of an anonymised dataset, extracted from the audit database held on NHS and University servers, did not require research ethics committee approval. Patients with ICH ascertained by LATCH, had the opportunity to consent to participate in the Lothian IntraCerebral Haemorrhage, Pathology, Imaging and Neurological Outcome (LINCHPIN) study, a prospective community-based research study examining the causes of ICH using brain MRI and research autopsy in case of death. The Scotland A Research Ethics Committee approved the study (10/MRE00/23).

Statistical analysis

We compared demographic, clinical and radiological characteristics in adults with lobar and non-lobar ICH using parametric statistics when characteristics conformed to a normal distribution and non-parametric statistics when they did not. For adults who underwent brain imaging (and were not diagnosed at autopsy) we calculated haematoma volume using the first CT brain scan after the adult's presentation with ICH using Quantomo computerised planimetry software (Cybertrial Inc, Calgary, Canada), which has been shown to have greater reliability for quantifying ICH volume in comparison to the ABC/2 method.[64,65]

We externally validated the ICH Score[8] for survival at one year. Because of small sample size bias potentially leading to over-estimation of odds ratios,[66] we repeated the multivariable analysis using a penalised maximum likelihood logistic regression [67](`firthlogit` command in Stata). Since the two models were very similar and the penalised regression model does not provide a goodness-of-fit statistic, we have reported the results of the original multivariable analysis. We assessed the performance of the ICH Score by calculating the area under a receiver operator characteristic curve (AUROC) using the values of the ICH score obtained for each participant.

We used a multivariable logistic regression model to assess whether lobar ICH location (with infratentorial as the referent category), age, Glasgow Coma Scale (GCS) score on admission, intraventricular extension, ICH volume and prior anticoagulant use were associated with survival at one year. We pre-specified these variables on the basis of their clinical relevance, known or hypothesised influences on outcome,[8,68] and the number of outcome events per variable since five to nine

outcome events per variable is valid, especially if variables are selected *a priori* and the associations found are plausible in the context of current knowledge.[69] We checked the calibration of the model using a likelihood ratio and Hosmer and Lemeshow's goodness of fit test which divides subjects into deciles based on predicted probabilities of case fatality and calculates a χ^2 statistic based upon observed and expected frequencies of deaths in each decile ($p > 0.05$ indicates that there is no significant difference between the observed and model-predicted values, implying that the model fits the data adequately).[70] Survival analyses of the time to an event started on the date of ICH symptom onset/detection and ended either on the date of the first event or on the date of censoring if no event occurred during follow-up. We censored follow-up on the date of death or one year after their ICH depending on which occurred first. For symptomatic outcome events, we calculated the total person-years of follow up using the sum of follow-up times irrespective of whether an event took place or whether the person was censored. For survival analyses, we quantified the completeness of follow-up by calculating the sum of follow-up times (days) divided by the sum of potential follow-up times which could have been obtained before death or the end of the one year follow-up period.[71] We used Kaplan-Meier survival curves and life tables with log rank tests and hazard ratios to analyse follow up data for outcome events during one-year follow-up. We conducted all analyses in Stata version 11.1.

Results

Of 166 adults with incident ICHs (Figure 1), the diagnosis of ICH was confirmed by brain CT in 162 (98%) cases and the rest were diagnosed at autopsy. 162 (98%) were

ascertained by one or more hot pursuit mechanisms. 30 (18%) also underwent brain MRI. Brain CT was done within two days of symptom onset in 144 (87%) cases. There were 25 secondary ICHs and 141 primary ICHs, of which 128 (91%) were first-ever-in-a-lifetime ICHs (Figure 1). The analyses of baseline characteristics and outcome after ICH are restricted to 128 first-ever ICHs.

The crude incidence of first-ever and recurrent spontaneous (primary and secondary) ICH in adults in the Lothian health board region of Scotland during 1st June 2010-31st May 2011 was 0.24 per 1000 per year (95% confidence interval [CI] 0.21 to 0.27). The incidence of first-ever spontaneous primary ICH was 0.18 per 1000 per year (95% CI 0.16 to 0.22) and the age-standardised incidence directly adjusted to the mid-2010 population estimates for the UK was 0.21 per 1000 per year (95% CI 0.20 to 0.21).. The incidence of both spontaneous first-ever lobar and non-lobar primary ICH increased across all age groups (Table I, online supplement). The overall incidence of lobar ICH was similar to non-lobar ICH (9.8 [95% confidence interval (CI) 7.7-12.4] versus 8.6 [95%CI 6.7-11.1] per 100,000 adults per year). The incidence of primary first-ever ICH associated with anti-thrombotic medication use was 0.09 per 1000 per year (95% CI 0.07 to 0.12).

Locations of haemorrhages in adults with first-ever spontaneous primary ICH

60 (47%) adults had non-lobar, spontaneous, primary, first-ever ICH (single non-lobar [n=59] and multiple non-lobar [n=1]), and the location of the remaining 68 (53%) was lobar (single lobar [n=61], single lobar extending to non-lobar regions [n=4], multiple lobar and non-lobar [n=2], and multiple lobar [n=1]).

Baseline characteristics of adults with first-ever lobar and non-lobar ICH

We compared the characteristics of adults with a spontaneous primary first-ever ICH (hereafter simply referred to as 'ICH') involving any lobar region to those with non-lobar ICH (Table 1). The proportion of adults with a past history of hypertension did not differ between those with lobar and non-lobar ICH (Table 1) and this was unchanged when the definition of hypertension was restricted to those taking antihypertensive medications at the time of the ICH (lobar 33 (49%) vs. non-lobar 29 (48%), χ^2 =0.01, p=0.92). A history of dementia was more common in adults with lobar ICH. The IQCODE was available for 47 (37%) adults, who were more likely to have reached further or higher education and less likely to have had an ischaemic stroke, but did not significantly differ in age or ICH location from adults without an IQCODE (Table II, Supplementary file). Admission GCS scores were significantly lower and ICH volumes were larger in the lobar ICH group. Extension of the ICH into the subdural and subarachnoid compartments was more common in the lobar ICH group.

Outcome after first-ever primary ICH

Completeness of one-year outcome data was 100% for vital status and 97% for dependence. By one year, 72 adults (56%, 95% CI 48-65%) had died and the proportions did not differ between lobar and non-lobar ICH (lobar 39/68 [57%]; non-lobar 33/60 [55%]), χ^2 =0.07, p=0.79). By one year, 107 (86%) adults were dead or dependent (modified Rankin scale score ≥ 3), but this proportion did not vary by ICH location (lobar 58/68 [88%] vs non-lobar 49/60 [84%]; χ^2 =0.30, p=0.58). Three adults underwent surgical intervention; two adults with lobar ICH underwent insertion

of a ventricular drain and one adult with a deep ICH underwent craniotomy and ICH evacuation.

Predictors of death in the first year

In a multivariable regression analysis of 122 adults with first-ever primary ICH using explanatory variables defined according to the ICH score, age (≥80 years), decreasing GCS on admission, ICH volume (≥30ml) and infratentorial ICH were the components of the ICH Score associated with death at one year (Table 2). In a sensitivity analysis using a penalised maximum likelihood logistic regression model, the results were unchanged (age ≥80 years OR 2.57, 95% CI 1.08-6.16; GCS 5-12 OR 2.56, 95% CI 1.00-6.61; GCS 3-4 OR 5.62, 95% CI 0.82-38.74 (using GCS 13-15 as the referent category); ICH volume >30ml OR 3.32, 95% CI 1.21-9.14; infratentorial ICH OR 5.70, 95% CI 1.18-27.53 and intraventricular extension OR 1.89, 95% CI 0.80-4.54). The AUROC was 0.82 (95% CI 0.74 to 0.89) indicating that the ICH Score discriminated well between those who survived and those who did not in the first year after first-ever ICH.

In a multivariable logistic regression analysis of 122 adults with first-ever primary ICH (Table 3), in comparison to infratentorial ICH, lobar ICH was associated with a 20-fold lower odds of death at one year (adjusted odds ratio [OR] 0.05, 95% CI 0.01 to 0.38) and deep ICH was associated with a six-fold lower odds of death, although this difference was not statistically significant (adjusted OR 0.16, 95% CI 0.02 to 1.26; p=0.08). Older age, lower GCS scores on admission and larger ICH volumes on brain imaging were also independent predictors of death. The model was well calibrated (Likelihood ratio test p<0.001; Hosmer and Lemeshow's goodness of fit test χ^2 =3.71, p=0.88). In a sensitivity analysis comparing lobar vs. non-lobar ICH,

one-year case fatality was lower after lobar ICH than after non-lobar ICH (adjusted OR for death at one year: lobar vs. non-lobar ICH 0.21, 95% CI 0.07 to 0.63; p=0.006, after adjustment for known predictors of outcome). In view of these findings, we reclassified location in the ICH Score as lobar, deep or infratentorial (with scores of 0,1 and 2 respectively) but this did not improve the discrimination of the ICH Score at one year (AUROC 0.82, 95% CI 0.75-0.89).

Recurrent ICH after primary ICH

During 63 person-years of follow-up (97% completeness at one year) there were four recurrent ICHs, all of which were in lobar locations following prior primary lobar ICH (annual risk of recurrent ICH after lobar ICH 11.8%, 95% CI 4.6% to 28.5% vs. annual risk after non-lobar ICH 0%; p=0.04; Figure II, online supplement).

Discussion

Adults with lobar ICH were more likely to have preceding dementia, a lower admission GCS score and larger ICHs with subarachnoid extension and subdural extension in comparison to those with non-lobar ICH. However, adults with lobar ICH were significantly more likely to survive one year compared to adults with non-lobar ICH after adjustment for other known predictors of outcome. The ICH Score discriminated well between those who survived and those who died in the first year after ICH. The risk of recurrent ICH was higher after lobar ICH.

We used a prospective, population-based design with multiple overlapping sources of case ascertainment and follow-up and a sample size sufficient to permit multivariable analyses. An experienced neuroradiologist with a special interest in stroke classified

all ICH locations in a multi-disciplinary meeting in which usually more than one neuroradiologist was present. There has been good inter-observer agreement in the assessment of supratentorial ICH location even for larger haematomas.[72] This is the first study to externally validate the ICH Score to determine one year survival in a population-based cohort.

The first year of this ongoing study has a small sample size, short follow up period and small number of outcome events. The multiple comparisons of baseline characteristics may have increased the likelihood of a statistically significant result occurring by chance. We obtained a history of dementia in all participants by reviewing their hospital and primary care records (although relatives completed the IQCODE questionnaire as well in only 37%). Adults without an IQCODE were more likely to have not reached further or higher education and have a past history of ischaemic stroke raising the possibility of underascertainment of premorbid dementia, but the proportion of participants with dementia was very similar to another cohort of participants with ICH [73]and since ICH location did not differ between participants for whom an IQCODE was obtained and others, any resulting misclassification of exposure is likely to have been non-differential. We did not adjust for premorbid conditions which might affect outcome,[74] but since most characteristics in both lobar and non-lobar ICH groups were similar it is unlikely that this affected the findings. Similarly, we did not adjust for the presence of subarachnoid extension,[75] as this is associated with a larger ICH volume which is likely to be the primary determinant of poor outcome.[76] We only categorised the presence or absence of intraventricular haemorrhage rather than determining the extent of it[77] and did not adjust for participants' do-not-resuscitation status which may influence outcome.[8]

We assessed intraventricular haemorrhage on the first (diagnostic) CT and therefore may have missed patients who had delayed intraventricular haemorrhage.[78]

We found the incidence of ICH to be comparable to the findings of a recent meta-analysis, in which the incidence had not changed for several decades.[1] The incidence of antithrombotic drug-associated ICH was comparable to that of another contemporary population-based cohort[7] and its frequency did not differ according to ICH location (Table 1).

Age and pre-morbid hypertension did not differ according to ICH location in our cohort, which is similar to the findings of other population-based studies.[79] Two[61][[73] of five hospital-based studies[32,45,51,61,73] have also found pre-morbid dementia to be more common in those with lobar ICH, which may reflect the higher prevalence of CAA underlying lobar ICH.

Lobar ICH has been associated with a better outcome in a population-based study,[11] but not in others,[14,17,18] which may be due to confounding. We found that lobar ICH location influenced survival and risk of recurrent ICH, independent of other known prognostic factors. Lobar ICHs may be associated with a better outcome in comparison to ICH in other locations, despite differences in ICH volume, because lobar anatomy and cortical atrophy,given the higher prevalence of pre-ICH dementia[73], may protect against mass effect resulting from ICH.

The risk of recurrent ICH in the lobar ICH group is similar to previous studies,[21] which may be due to the prevalence of CAA in lobar regions,or perhaps due to the severity of other vasculopathies in survivors of deep ICH.

Since patients with lobar ICH are more likely to survive, but are also at higher risk of ICH recurrence (Figure II, online supplement),[80-82], secondary prevention with antihypertensive drugs[83] may be particularly relevant to this group of patients.

Larger studies could examine the influence of biomarkers of CAA[84,85] and other causes of ICH[86] on outcome and recurrent ICH. Since survivors of ICH have higher mortality in comparison to the general population[87] and given the apparently higher risk of ICH recurrence after lobar ICH (Figure II, online supplement),[21] treatments directed at the specific small vessel diseases underlying ICH, such as CAA, may improve outcome (Study Evaluating the Safety, Tolerability and Efficacy of PF-04360365 in Adults With Probable Cerebral Amyloid Angiopathy", NCT01821118).

Acknowledgements

We are grateful to Rosemary Anderson, Aidan Hutchison, collaborators and the adults included in the audit. The imaging was carried out at the Brain Research Imaging Centre, Neuroimaging Sciences, Edinburgh (www.bric.ed.ac.uk), University of Edinburgh, which is part of the SINAPSE collaboration (www.sinapse.ac.uk) funded by the Scottish Funding Council and the Chief Scientist Office. Support from NHS Lothian R&D and the Wellcome Trust Clinical Research Facility are gratefully acknowledged.

Funding

NS is funded by an MRC/TSA Clinical Research Training Fellowship. AF is funded by a grant from the European Erasmus Program. JMW was part supported by the

Scottish Funding Council through the Scottish Imaging Network - A Platform for Scientific Excellence (SINAPSE) Collaboration. RA-SS is funded by an MRC Senior Clinical Fellowship.

Disclosures

None

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Figures

Figure 1

Flowchart of adults with spontaneous ICH included in the study

Table 1

	Lobar ICH (n=68)	Non-lobar ICH (n=60)	p value
Sex (male), (%)	26 (38)	29 (48)	0.25
Age (years); median (IQR)	79 (15)	76 (19)	0.84
History of hypertension*			
Yes (n, %)	40 (59)	41 (68)	0.21
History of diabetes*			
Yes (n, %)	5 (7)	8 (13)	0.25
History of dementia			
Yes (n, %)	14 (21)	3 (5)	0.01
History of smoking*			
Never (n, %)	30 (44)	26 (43)	
Ex-smoker (n, %)	20 (29)	24 (40)	
Current (n, %)	17 (25)	10 (17)	0.40
Alcohol consumption[$]	2 (0-14)	4 (0-14)	0.70
Premorbid medication			
Antiplatelet use* (n, %)	28 (41)	19 (32)	0.24
Anticoagulant use (n, %)	8 (12)	10 (17)	0.43
Admission GCS score** median (IQR)	13 (9-14)	14 (10-15)	0.03
Admission systolic blood pressure (mmHg)^ mean (SD)	117 (28)	123 (23)	0.22
ICH volume (ml)^^ median, (IQR)	38 (17-74)	11 (4-25)	<0.001
Intraventricular extension^^ Yes (n, %)	33 (51)	31 (53)	0.85
Subarachnoid extension^^ Yes (n, %)	37 (57)	3 (5)	<0.001
Subdural extension^^ Yes (n, %)	10 (15)	2 (3)	0.02

*Data missing for one adult
[$]average number of units per week (median; IQR); data missing in 9 cases
** data missing in five cases (three of whom died in the community)
^ data missing in 12 cases (three of whom died in the community)
^^data missing in four cases for whom the diagnosis was confirmed at autopsy

Table 2

Variable	Adjusted OR, 95% CI	p
Age (≥80 years)	2.75 (1.11-6.80)	0.03
Glasgow coma scale		
13-15	1.00	
5-12	2.71 (1.01-7.26)	0.048
3-4	8.18 (0.86-78.15)	0.07
ICH volume (≥ 30ml)	3.57 (1.25-10.21)	0.02
Infratentorial ICH	7.15 (1.29-39.75)	0.03
Presence of intraventricular extension	0.51 (0.20-1.25)	0.14

Table 3

Variable	Adjusted OR, 95% CI	p
Increasing age (per year)	1.07 (1.03-1.11)	0.001
Increasing Glasgow coma scale score (per point)	0.81 (0.67-0.97)	0.02
Increasing ICH volume (per ml)	1.05 (1.02-1.08)	0.001
ICH location		
Infratentorial	1.00	
Deep	0.16 (0.02-1.26)	0.08
Lobar	0.05 (0.01-0.38)	0.01
Presence of intraventricular extension	0.61 (0.22-1.75)	0.36
Anticoagulant use at presentation with ICH	1.56 (0.30-7.97)	0.60