Baseline factors associated with early and late death in intracerebral haemorrhage survivors

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Article type : Original Article

BASELINE FACTORS ASSOCIATED WITH EARLY AND LATE DEATH IN INTRACEREBRAL HAEMORRHAGE SURVIVORS

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ENE.14238

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Word count: **3663** words
Running title: Associations of early and late death in ICH survivors
Key words: Intracerebral haemorrhage; Mortality; Prognosis

FUNDING

The CROMIS-2 study is funded by the Stroke Association and British Heart Foundation. GB holds a National Institute for Health Research (NIHR) Academic Clinical Fellowship, and received funding from the Rosetrees Trust. GA receives funding from the NIHR UCLH Biomedical Research Centres (BRC). TY is supported by grants from the Medical Research Council, MS Society of Great Britain and Northern Ireland, Stroke Association, British Heart Foundation and Wellcome Trust. MMB's Chair in Stroke Medicine is supported by the Reta Lila Weston Trust for Medical Research. DJW receives support from the Stroke Association, British Heart Foundation and Rosetrees Trust. This work was undertaken at UCLH/UCL which receives a proportion of funding from the Department of Health's NIHR BRC funding scheme.

DISCLOSURES

HC reports grants and other support from Bayer Healthcare and from UCB, outside the submitted work. TY reports personal fees and other support from GlaxoSmithKline, Biogen Idec, Novartis, ESOR, Merck, Hikma, and Parexel, outside the submitted work; .GYHL reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo outside the submitted work; no fees are directly received personally. KM reports personal fees from Bayer, personal fees and non-financial support from Boehringer Ingelheim, and personal fees from Daiichi-Sankyo, outside the submitted work. DJW reports personal fees from Bayer, personal fees from Alnylam, and personal fees from Portola, outside the submitted work.The remaining authors report no disclosures or conflicts of interest relevant to the manuscript.

ABSTRACT

Background:

We wished to determine whether early and late death are associated with different baseline factors in intracerebral haemorrhage survivors.

Methods:

This is a secondary analysis of the multicentre prospective observational CROMIS-2 ICH study. Death was defined as "early" if occurring within 6 months of study entry, and "late" if occurring after this time point.

Results:

In our cohort (n=1094), there were 306 deaths (per 100 patient-years: absolute event rate 11.7, 95% CI 10.5 to 13.1); 156 were "early" and 150 "late". In multivariable analyses, early death was independently associated with age (per year increase, HR 1.05, p=0.003), history of hypertension (HR 1.89, p=0.038), pre-event mRS (per point increase, HR 1.41, p<0.0001), admission NIHSS (per point increase, HR 1.11, p<0.0001), and haemorrhage volume > 60ml (HR 4.08, p<0.0001). Late death showed independent associations with age (per year increase, HR 1.04, p=0.003), pre-event mRS (per point increase, HR 1.42, p=0.001), prior anticoagulant use (HR 2.13, p=0.028) and the presence of intraventricular extension (HR 1.73, p=0.033) in multivariable analyses. In further analyses where time was treated as continuous (rather than dichotomised), the hazard ratio of previous cerebral ischaemic events increased with time, whilst those for GCS, NIHSS and ICH volume decreased over time.

Conclusions:

We provide new evidence that not all baseline factors associated with early mortality after intracerebral haemorrhage are associated with mortality after 6 months, and that the effects of baseline variables change over time. Our findings could help design better prognostic scores for later death after intracerebral haemorrhage.

INTRODUCTION

Most research on outcomes following intracerebral haemorrhage (ICH) has focussed on short term mortality (within 6 months), reflecting the high rates of early death associated with this stroke subtype(1, 2). Many factors associated with early mortality relate to ICH severity, and this is reflected in prognostic scores which aim to predict outcome in the short term(3-11). Policies of active acute management including blood pressure lowering, prompt reversal of anticoagulation, and neurosurgical referral aim to improve prognosis in patients with ICH(12); an improved understanding of the factors that influence "late" death following ICH might identify potentially modifiable risk factors that could improve long term outcomes(1).

Our aim was to evaluate whether early and late death are associated with different baseline factors in intracerebral haemorrhage survivors using data from the prospective multicentre CROMIS-2 ICH study. We hypothesised that factors relating to the severity of the acute ICH would not be associated with death at later (beyond 6 months) time points.

METHODS

Data availability

Analyses for the CROMIS-2 study are ongoing; once all of these analyses are completed, the CROMIS-2 Steering Committee will consider applications from other researchers for access to anonymised source data.

Participants

We included adults from the CROMIS-2 ICH study (Clinical Relevance of Microbleeds in Stroke); full details of the study protocol have been published previously(13). Further details are provided in the Supplementary Methods. The study was approved by the National Research Ethics Service (IRAS reference 10/H0716/61). Informed written consent was obtained for all participants.

Outcomes

The outcome of interest for this project was time to death. Mortality notifications were received from NHS Digital (previously the Health and Social Care Information Centre) as detailed in the previously published study protocol(13). NHS Digital is a national centralised body that collects data on health and social care in the United Kingdom; mortality data are derived from "hospital episode statistics" (records of all NHS patient admissions) and information on registered deaths from the Office of National Statistics (death registration is a legal requirement in the United Kingdom).

Patients were censored at either 3 years following the ICH that resulted in study entry, or at last available follow-up for vital status (the time of the study's last notification of deaths from NHS Digital: October 31, 2017), depending on which was earlier.

Imaging

Brain CT imaging was acquired acutely at the time of the index event as part of the patient's routine clinical care. Further details are provided in the Supplementary Material.

Statistics

Statistical analysis was performed using Stata (Version 15.1). We dichotomised time following ICH into "early" (before 6 months) and "late" (after 6 months) periods. We used univariable Cox regression to calculate hazard ratios (HR) for all baseline variables collected to review for associations during these two time periods. Variables where the 95% confidence intervals (CI) did not cross 1 were considered as statistically significant. To explore this further, the effect of each baseline variable was then allowed to vary linearly with time; further details are provided in the Supplementary Material.

RESULTS

All 1094 patients recruited to CROMIS-2 ICH were included (Table 1). Follow up was for a total 2613.48 patient-years (median 3.00 years, interquartile range, IQR, 2.31 to 3.00 years). There were 306 deaths (absolute event rate 11.7 per 100 patient-years, 95% CI 10.5 to 13.1 per 100

patient-years; Figure 1). The median time between the index ICH event and study entry was 4 days (IQR 2 to 8 days).

Associations of "early" vs "late" death

Of the 306 deaths, 156 occurred within 6 months of the index haemorrhage event ("early"), and 150 deaths occurred after 6 months and within 3 years of the index ICH ("late"). Baseline characteristics for both groups are shown in Table 1.

Early death (Table 2) was associated with age, hypertension, diabetes mellitus, atrial fibrillation (AF), a history of previous cerebral ischaemic events, pre-event modified Rankin scale (mRS), anticoagulant use prior to ICH, Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS) scores at study entry. Imaging features at study entry that were significantly associated with early death were Van Swieten score, ICH volume, and the presence of intraventricular extension. In a multivariable model including these variables, age at study entry (per year increase, HR 1.05, 95% CI 1.02 to 1.08, p=0.003), history of hypertension (HR 1.89, 95% CI 1.04 to 3.46, p=0.038), pre-event mRS (per point increase, HR 1.41, 95% CI 1.17 to 1.70, p<0.0001), admission NIHSS (per point increase, HR 1.11, 95% CI 1.06 to 1.15, p<0.0001), and ICH volume > 60ml (HR 4.08, 95% CI 1.85 to 8.96, p<0.0001) remained associated with early death.

When considering death later than 6 months (Table 2), age, AF, smoking, pre-event cognitive impairment, previous cerebral ischaemic event, pre-event mRS, anticoagulant use prior to index ICH, increasing van Swieten score and the presence of intraventricular extension showed significant associations. In a multivariable model including all variables with a significant association with late death, only age at study entry (per year increase, HR 1.04, 95% CI 1.02 to 1.08, p=0.003), pre-event mRS (per point increase, HR 1.42, 95% CI 1.16 to 1.73, p=0.001), anticoagulant use prior to ICH (HR 2.13, 95% CI 1.08 to 4.17, p=0.028) and the presence of intraventricular extension (HR 1.73, 95% CI 1.05 to 2.85, p=0.033) remained associated with late death.

We then investigated which baseline characteristics showed a significant change in HR between the early and the late periods (Table 2). We found that HRs for the presence of *APOE* ε2, GCS, NIHSS, and ICH volume > 60ml showed evidence of significant change between the early and late periods (Table 2).

Further exploratory analysis of time-varying effects

We then performed exploratory analyses where, time was considered as a continuous measure (Supplementary Table 1). In these analyses, variables which showed significant time-varying effects were history of a previous cerebral ischaemic event ($p=0.0214$), admission GCS ($p=0.0108$), NIHSS ($p<0.00001$) and ICH volume ($p=0.0439$). The hazard ratios of previous cerebral ischaemic events increased with time, whilst those for NIHSS and ICH volume decreased with time. The protective (negative association) of GCS also decreased with time.

DISCUSSION

We provide new evidence that not all baseline factors associated with early mortality after intracerebral haemorrhage are associated with mortality after 6 months. In analyses where the time-varying effect of baseline variables were allowed to vary continuously with time, we found that the influence of measures of acute intracerebral haemorrhage severity decreased over time, whereas those associated with established cerebrovascular disease (previous cerebral ischaemic events) increased over time. These results support the argument that definitions of "early" or "late" death are necessarily arbitrary, as the impact of some characteristics present at study entry vary continuously with time.

In our study, the factors that we found were independently associated with early death are in keeping with other studies, and reflected in pre-existing prognostic scores which include these and other variables(4-11). Differences between our results for associations with late death and those previously reported(14, 15) are likely to reflect our method of considering early and late death independently; when considering all death events together, we observed similar effects to those previously reported. Additionally, we observed that four variables (*APOE* ε2, GCS, NIHSS and ICH volume > 60ml) showed significant differences in the magnitude of their effect before and

after 6 months (although the hazard ratios for *APOE* ε2 were not statistically significant in themselves). This result confirms that whilst GCS, NIHSS and ICH volume are important predictors of early mortality, their effect changes significantly between the early and late periods, and thus they are less useful for predicting mortality in the longer-term, as we hypothesised. Our analyses of linear time-varying effects on long term mortality following ICH are novel and demonstrate the potentially complex interactions that can occur over time. These analyses highlight the difficulties in defining what is "early" death, or a "short-term" outcome; further work that considers time-varying effects on mortality across longer time scales is needed to guide this.

Our finding of an association between intraventricular extension with late death seems counterintuitive, but illustrates the importance of our work and the complicated manner in which baseline variables might interact over time. Given that our cohort included patients with milder strokes, we hypothesise that the effect of intraventricular extension on early death was lost in the adjusted analyses because of larger magnitude effects associated with other factors associated with ICH severity (NIHSS and ICH volume). We speculate when considering late death, the effects of acute factors such as NIHSS and ICH volume were of smaller magnitude, and thus the impact of intraventricular extension as a measure of stroke severity became more apparent. We did observe, in unadjusted analyses, that intraventricular extension was associated with both early and late death, but the magnitude of the association was smaller for late death (Table 2).

Our study has a number of strengths, including the number of patients, its multicentre design (which increases generalisability), robust ascertainment of follow up events and the detailed clinical and radiological data available for each participant. However, there are limitations of our work. Our cohort is comprised of survivors with mild strokes, as reflected by the median NIHSS and GCS scores, low ICH volumes and low early death rates. This cohort therefore is unlikely to be representative of all ICH patients, particularly those with more severe haemorrhages. We were unable to adjust for acute complications of ICH, or details relating to immediate care, either active or care-limiting (do not resuscitate orders or palliative pathways), all of which would impact mortality. Additionally, we were unable to comment on cause of death in our patients. Finally, whilst we considered the time-varying effects of variables recorded at study entry, the status of these may have changed after this time-point (for example, anti-platelet or anticoagulant use) and this could have influenced our results.

We provide new evidence that not all baseline factors associated with early mortality after intracerebral haemorrhage are associated with mortality after 6 months.. Our findings could help design better prognostic scores for later death after intracerebral haemorrhage.

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TABLES

Table 1: Baseline characteristics

Percentage values were calculated using the total number of patients for whom data were available as the denominator.

	All	Alive	Early death (<6 months)	Late death (≥6 months)
n	1094	788 (72.0)	156 (14.3)	150 (13.7)
Age, years, mean (SD)	73.3 (12.5)	70.3 (12.4)	81.1 (9.4)	80.7 (8.5)
Sex, male, n (%)	628 (57.4)	468 (59.4)	78 (50.0)	82 (54.7)
Hypertension, n (%)	718 (66.7)	505 (65.3)	114 (73.6)	99 (66.9)
Hypercholesterolaemia, n (%)	467 (44.0)	322 (42.0)	71 (47.7)	74 (50.3)
Diabetes mellitus, n (%)	202 (18.6)	132 (16.9)	38 (24.4)	32 (21.6)
AF, n (%)	375 (37.4)	215 (30.1)	81 (56.3)	79 (55.2)
Smoking (at time of ICH), n (%)	114 (10.8)	94 (12.4)	12 (8.0)	8 (5.6)
Pre-existing cognitive impairment, n (%)	251 (39.8)	150 (34.3)	54 (50.5)	47 (54.7)
Previous cerebral ischaemic event, n (%)	241 (22.9)	149 (19.5)	44 (30.1)	48 (33.8)
Previous ICH, n (%)	46 (4.3)	28 (3.6)	10 (6.7)	8 (5.6)
Pre-event mRS, median (IQR)	0 (0 to 1)	0 (0 to 1)	1 (0 to 3)	1 (0 to 2)
APOE ε2, presence, n (%)	189 (20.7)	138 (20.8)	31 (26.5)	20 (15.3)
APOE ε4, presence, n (%)	256 (28.1)	196 (29.5)	24 (20.5)	36 (27.5)
Medications				
Anti-platelet use prior to ICH, n (%)	267 (24.6)	193 (24.7)	38 (24.5)	36 (24.2)
Anticoagulant use prior to ICH, n (%)	436 (40.1)	261 (33.4)	86 (55.5)	89 (59.3)
Anti-platelet at discharge, n	65 (6.4)	46 (6.2)	8 (6.2)	11 (7.8)

(%)					
Anticoagulant at discharge, n (%)		113 (10.7)	78 (10.2)	14 (9.5)	21 (14.5)
Clinical features at study entry					
GCS, median (IQR)		15 (14 to 15)	15 (14 to 15)	14 (11 to 15)	15 (14 to 15)
NIHSS, median (IQR)		7 (3 to 13)	6 (3 to 11)	14 (7 to 19)	6 (3 to 12)
Imaging features at study entry					
Lacunes, presence, n (%)		98 (9.0)	69 (8.8)	15 (9.6)	14 (9.3)
Van Swieten Score (WMC), median (IQR)		0 (0 to 2)	0 (0 to 2)	1 (0 to 3)	2 (0 to 3)
ICH location	Infratentorial	99 (9.1)	69 (8.8)	12 (7.7)	18 (12.0)
	Deep	546 (50.0)	398 (50.6)	69 (44.2)	79 (52.7)
	Lobar	447 (40.9)	319 (40.6)	75 (48.1)	53 (35.3)
ICH volume	<30ml	886 (85.9)	655 (89.0)	106 (70.7)	125 (85.6)
	30 – 60ml	99 (9.6)	60 (8.2)	24 (16.0)	15 (10.3)
	>60ml	47 (4.6)	21 (2.9)	20 (13.3)	6 (4.1)
IV extension		301 (27.7)	183 (23.4)	68 (43.6)	50 (33.6)

Table 2: Univariable Cox regression analysis for early (before 6 months) and late (after 6 months) periods following ICH

Univariable hazard ratios for each characteristic obtained by fitting Cox regression models with time-varying effects (before/after 6 months). The time-varying coefficient p value compares the difference between the early and the late hazard ratios.

	"Early" , HR (95% CI)	**"Late", HR (95% CI)**	**Time-varying coefficient, p value**
Age, per year increase	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.11)	0.360
Sex, male	0.73 (0.53 to 1.00)	0.85 (0.62 to 1.18)	0.500
Hypertension	1.43 (1.00 to 2.04)	1.08 (0.77 to 1.52)	0.270
Hypercholesterolaemia	1.18 (0.86 to 1.63)	1.34 (0.97 to 1.85)	0.585
Diabetes mellitus	1.44 (1.00 to 2.07)	1.31 (0.89 to 1.94)	0.729
AF	2.31 (1.66 to 3.21)	2.67 (1.92 to 3.71)	0.548
Smoking, current	0.70 (0.39 to 1.27)	0.45 (0.22 to 0.91)	0.337
Pre-existing cognitive impairment	1.32 (0.75 to 2.34)	2.13 (1.39 to 3.25)	0.336
Previous cerebral ischaemic event	1.50 (1.05 to 2.13)	1.90 (1.34 to 2.69)	0.345
Previous ICH	1.65 (0.87 to 3.14)	1.49 (0.73 to 3.04)	0.833
Pre-event mRS, per point increase	1.56 (1.40 to 1.74)	1.50 (1.33 to 1.69)	0.610
APOE ε2, presence	1.40 (0.93 to 2.11)	0.70 (0.44 to 1.13)	0.032
APOE ε4, presence	0.65 (0.42 to 1.02)	0.90 (0.61 to 1.32)	0.280
Medications			
Anti-platelet use prior to ICH	0.98 (0.68 to 1.42)	0.96 (0.66 to 1.40)	0.936
Anticoagulant use prior to	1.97 (1.44 to 2.71)	2.73 (1.97 to 3.78)	0.164

ICH				
Anti-platelet at discharge		0.95 (0.46 to 1.93)	1.23 (0.67 to 2.28)	0.582
Anticoagulant at discharge		0.85 (0.49 to 1.48)	1.48 (0.93 to 2.35)	0.134
Clinical features at study entry				
GCS, per point increase		0.80 (0.76 to 0.84)	0.93 (0.86 to 1.00)	0.001
NIHSS, per point increase		1.11 (1.08 to 1.14)	1.00 (0.97 to 1.04)	<0.0001
Imaging features at study entry				
Lacunes, presence		1.05 (0.62 to 1.79)	1.06 (0.61 to 1.84)	0.976
Van Swieten Score (WMC), per point increase		1.23 (1.11 to 1.36)	1.37 (1.23 to 1.51)	0.139
ICH location	Infratentorial	*Reference group*		
	Deep	1.04 (0.57 to 1.93)	0.79 (0.47 to 1.32)	0.494
	Lobar	1.42 (0.77 to 2.62)	0.67 (0.39 to 1.14)	0.067
ICH volume	<30ml	*Reference group*		
	30 – 60ml	2.20 (1.41 to 3.42)	1.29 (0.75 to 2.20)	0.131
	>60ml	4.85 (3.01 to 7.83)	1.40 (0.62 to 3.18)	0.010
IV extension		2.20 (1.61 to 3.02)	1.55 (1.11 to 2.18)	0.141

FIGURES

Figure 1: Unadjusted cumulative mortality curve

APPENDIX

The CROMIS-2 collaborators:

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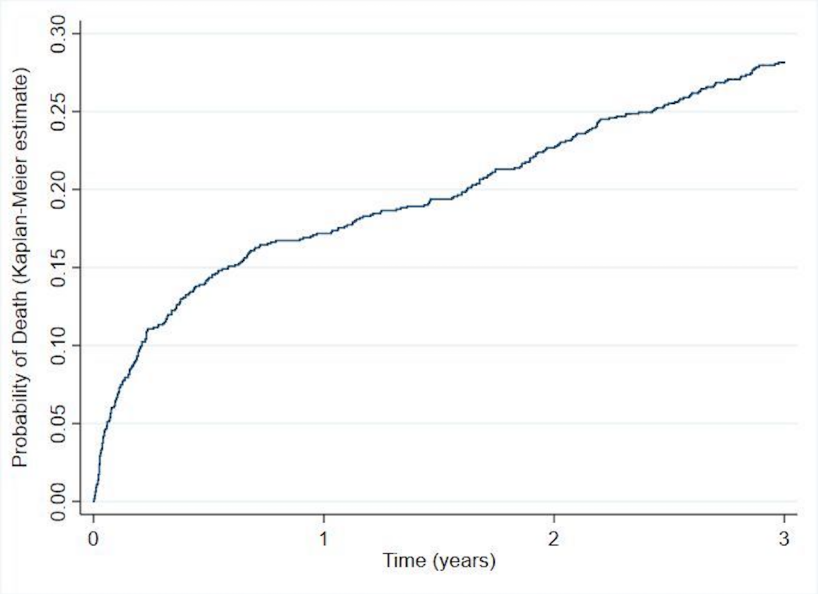

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