Cerebral small vessel disease and functional outcome prediction after intracerebral haemorrhage

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Keywords. Intracerebral haemorrhage, long-term functional outcome, small vessel disease, CT

ABSTRACT

Background. It is unknown whether adding cerebral small vessel disease (SVD) biomarkers can improve the performance of intracerebral hemorrhage (ICH) outcome predictive scores.

Purpose. To determine whether: (1) CT-based SVD biomarkers are associated with 6-month functional outcome after ICH and (2) whether these biomarkers improve the performance of pre-existing ICH score.

Methods. We included 864 patients with acute ICH from a multicentre, hospital-based prospective cohort study. We evaluated CT-based SVD biomarkers (white matter hypodensities [WMH]; lacunes; brain atrophy; and a composite SVD burden score) and their associations with poor 6-month functional outcome (modified Rankin Scale [mRS] score >2). The area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow test were used to assess discrimination and calibration of the ICH score with and without SVD biomarkers.

Results. In multivariable models (adjusted for ICH score components), WMH presence (OR 1.52, 95%CI 1.12-2.06), cortical atrophy presence (OR 1.80, 95%CI 1.19-2.73), deep atrophy presence (OR 1.66, 95%CI 1.17-2.34), and severe atrophy (either deep or cortical) (OR 1.94, 95%CI 1.36-2.74) were independently associated with poor functional outcome. For the ICH score, the AUROC was 0.71 (95%CI 0.68-0.74). Adding SVD markers did not significantly improve ICH score discrimination; for the best model (adding severe atrophy) the AUROC was 0.73 (95%CI 0.69-0.76). These results were confirmed when considering lobar and non-lobar ICH, separately.

Conclusions. The ICH score has acceptable discrimination for predicting 6-month functional outcome after ICH. CT biomarkers of SVD are associated with functional outcome but adding them does not significantly improve ICH score discrimination.

INTRODUCTION

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) is a devastating form of stroke, with 40% mortality at 30 days and 65% at one year [1], [2]. Only about 20% of survivors are functionally independent at 6 months [3], [4]. In order to plan clinical care and provide prognostic information, it is essential to understand which baseline factors, available in the acute phase, are associated with functional outcome. Several clinical-radiological scores have been developed to predict functional outcome or mortality after ICH at different time-points (usually 30 or 90 days). Subsequent studies have validated existing scores for different outcomes at different time-points[5]. The ICH score [6] (Table e-1) is the most commonly used and extensively validated predictive score [5]. The score (range 0–6) is the sum of points assigned to five variables: Glasgow Coma Scale score 3–4 (2 points) or 5–12 (1 point); age ≥ 80 years (1 point); infratentorial site (1 point); ICH volume ≥ 30 mL (1 point); and intraventricular hemorrhage (1 point).

Cerebral small-vessel disease (SVD) includes deep perforator (hypertensive) arteriopathy and cerebral amyloid angiopathy (CAA), which are considered extremes along a continuum of age-related pathologies[7]. SVD causes around 77% of spontaneous ICH[8], can readily be assessed using neuroimaging markers on both magnetic resonance imaging (MRI) and computed tomography (CT) scans, and is associated with functional outcome and cognitive decline[9] after stroke[10]. It is not known whether SVD burden can improve the prediction performance of existing clinical-radiological scores for functional outcome after ICH.

In a large multicentre UK ICH cohort, we aimed to investigate the association of CT-based SVD biomarkers with 6-month functional outcome and to assess whether these improve the predictive performance of the ICH score.

MATERIAL AND METHODS

Study population

We included data from the CROMIS-2 (ICH), a prospective cohort study of adult patients with spontaneous, non-traumatic ICH (NCT02513316) undertaken at 79 UK hospitals (and one in the Netherlands). We included participants with: (1) all variables required for calculation of the ICH score (Glasgow Coma Score [GCS], ICH volume, ICH location [supratentorial or infratentorial], age [≥80 or <80], and presence of intraventricular haemorrhage); (2) functional outcome recorded at 6 months using the modified Rankin Scale (mRS, dichotomized into 0-2 [good functional outcome] and 3-6 [poor functional outcome]); and (3) baseline acute brain CT of adequate quality to evaluate all SVD biomarkers. We excluded patients with a known underlying structural cause for ICH (arteriovenous malformation, tumour, cavernomas, intracranial aneurysm, or haemorrhagic transformation of an infarct). We collected detailed data on demographics, risk factors, clinical presentation and brain imaging findings.

Standard Protocol Approvals, Registrations and patient consents. Written informed consent was obtained from all participants; in case of lack of capacity written informed consent was obtained from a relative or representative.

Ethical approval and data availability. The CROMIS-2 study was approved by the local Ethics Committee (reference: 10/H0716/64). All data requests should be submitted to the corresponding author for consideration by the CROMIS-2 Steering Committee. Supplementary data (Tables e-1-e-3)) are available from Dryad https://doi.org/10.5061/dryad.ksn02v72s.

CT variables: selection, measurement and categorization

Measurement of ICH volume was performed via a semi-automated (threshold-based) approach, as previously described[11]. ICH location was assessed using the Cerebral Haemorrhage Anatomical Rating Instrument (CHARTS)[12]. Two experienced trained raters (DS and DW) assessed the presence and severity of CT-based markers of SVD[13], [14], [15] [16] including: white matter hypodensities (WMH), lacunes, cortical atrophy, deep atrophy and SVD burden. WMH (also termed leukoaraiosis) were rated according to the Van Swieten Scale[17] which combines posterior (range 0-2) and anterior (0-2) scores into an ordinal scale (0-4). WMH were considered severe if the Van Swieten scale was ≥2 in either anterior or posterior periventricular white matter. WMH were dichotomized as: 1) present (Van Swieten ≥1 [either anterior or posterior]) vs absent (Van Swieten = 0); and 2) severe vs non-severe. Lacunes were defined as round/ovoid, subcortical, fluid-filled cavities of 3-15 mm diameter, consistent with a previous infarct or haemorrhage[13]; ≥2 lacunes were considered severe [14]. As previously described[14] [15] [16], we evaluated deep (enlargement of the ventricles) and superficial (enlargement of the sulci) cerebral atrophy using a template based three-point scale (absent/mild, moderate and severe). Atrophy was considered severe if it was graded as severe in either deep or cortical regions. A SVD burden score was calculated as previously described[14]: one point was assigned for: (1) severe WMH; (2) severe (≥2) lacunes; and (3) presence of severe deep or cortical atrophy, giving a 4-point ordinal score (0-3). To evaluate the rater accuracy and reliability of CT scan assessment, both raters independently rated a random sample of 50 CT scans. The SVD burden score was considered severe if the score was ≥ 2. All ratings were blinded to outcome and all other patient clinical information.

Statistical analysis

We described categorical variables with frequencies and percentages, and continuous variables using mean and standard deviation (SD) or median with interquartile range (IQR). In univariable analysis, we used Chi-square and Wilcoxon/Mann–Whitney tests as appropriate.

We first investigated the predictive performance of the ICH score and whether this could be improved through simple re-calibration (linear transformation of the predicted log-odds achieved through logistic regression). Next, we considered whether more complicated re-calibration was necessary (re-estimation of all model coefficients using logistic regression).

We evaluated associations between all radiological and clinical variables (components of the ICH score as well as all CT-based SVD markers) with 6-month functional outcome using univariable analysis. We then constructed multivariable models for the associations of each SVD biomarker individually, and for a SVD burden score, adjusted for ICH score variables (GCS, ICH volume, ICH location [supratentorial or infratentorial], age [≥80 or <80], and presence of intraventricular haemorrhage) with poor 6-month functional outcome.

We then investigated whether we could improve the predictive performance for functional outcome of the ICH score through sequential addition of SVD markers found to be significantly associated with outcome in the univariable analysis; this analysis was performed in the entire cohort and in lobar and in non-lobar cohorts, separately. We also did a a sensitivity analysis using mRS>3 as the definition of poor functional outcome.

Discrimination and calibration were assessed for each predictive model. We assessed discrimination by calculating the area under the receiver operating characteristic curve

(AUROC). Calibration refers to the ability of a score to accurately predict the percentage of patients with the outcome of interest[18]. Inter-rater accuracy was evaluated via the proportion of agreement and Cohen's kappa statistic. We assessed calibration using the Hosmer-Lemeshow (HL) goodness-of-fit statistic: p-value < 0.05 is suggestive of poor calibration. We adjusted all AUROC results for optimism, using the bootstrap. The significance level was set at p=0.05. Statistical analysis was performed using STATA 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LP).

RESULTS

Of the original cohort of patients included in the CROMIS-2(ICH) study with available CT scan (n=1037), we excluded 173 patients from our analysis: 52 did not have all variables needed to calculate the ICH score, and 121 did not have 6-month follow-up data (Figure 1). We included 864 patients; Table 1 summarizes the patient characteristics, outcomes and imaging variables. There were no statistically significant differences between included and excluded patients for any of the variables of interest (data not shown). Mean age was 73.6 years (SD 11.9). The majority of patients suffered from hypertension (580; 67.1%). 429 patients had a deep ICH (49.6%), 361 (41.8%) lobar ICH and 74 (8.6%) infratentorial ICH. The mean ICH volume was 14.9 cm^3 (SD 20.2 cm^3), and 256 (29.6%) of patients had accompanying intraventricular haemorrhage. WMH was severe in 261 (30.2%) of patients, SVD burden score was moderate-to-severe in 124 (14.3%) patients, while 258 (29.9%) had severe atrophy. 535 patients (61.9%) had poor functional outcome (mRS >2) at 6 months. Inter-rater reliability for SVD biomarkers was as follows: atrophy 84.0% agreement, Cohen’s kappa 0.68; WMH 79.6% agreement, Cohen’s kappa 0.52; lacunes 95.0% agreement, Cohen’s kappa 0.45.

Discrimination and calibration of the ICH score

The discrimination of the ICH score for functional outcome at 6 months, measured by the AUROC, was 0.70 (95% CI 0.67-0.74) (Figure 2A). After simple re-calibration, good agreement between observed and expected event rate was achieved (HL p = 0.26) (Figure 2B). After recalculation of β-coefficients for each variable included in the score (Table 2), the revised model demonstrated an AUROC of 0.71 (95% CI 0.68-0.74). This new model showed improved calibration (HL p = 0.94).

Association between clinical-radiological variables and 6-month outcome

In the univariable analysis (Table 3), all variables included in the ICH score were associated with 6-month functional outcome, except for ICH location (supratentorial vs infratentorial, p = 0.296). With regards to CT biomarkers of SVD, WMH presence (OR 1.80, 95% CI 1.36-2.37, p <0.001), severe WMH (OR 1.48, 95% CI 1.09-2.01, p = 0.012), cortical atrophy (moderate OR 1.88, 95% CI 1.29-2.76, p = 0.001; severe OR 4.41, 95% CI 2.65-7.35, p < 0.001), deep atrophy (moderate OR 1.70, 95% CI 1.23-2.35, p = 0.001; severe OR 3.32, 95% CI 2.16-5.11, p <0.001), severe atrophy (OR 2.36, 95% CI 1.70-3.26, p <0.001) and severe SVD burden (OR 1.84, 95% CI 1.20-2.81, p = 0.004) were all associated with 6-month functional outcome.

After adjusting for variables in the ICH score (Table 4), presence of WMH (OR 1.52, 95% CI 1.12-2.06, p = 0.007), cortical atrophy (OR 1.80, 95% CI 1.19-2.73, p = 0.006), deep atrophy (OR 1.66, 95%CI 1.17-2.34, p = 0.004), severe atrophy (OR 1.94, 95% CI 1.36-2.7, p <0.001) were associated with 6-month functional outcome. In adjusted analysis, severe SVD burden score showed a non-significant association with 6-month outcome (OR 1.57 [95%CI 0.99-2.48]; p =

0.053). The presence of severe atrophy was strongly associated with 6-month functional outcome, even after adjusting for other severe SVD markers and variables present in the ICH score (OR 2.22, 95% CI 1.41-3.52, p = 0.001).

Addition of CT-based makers of SVD to ICH score

When individually added to the revised ICH score model, WMH presence, cortical atrophy, deep atrophy, severe atrophy and severe SVD burden score did not significantly improve discrimination, as shown in Table 5; although an increase in the AUC was noted, but the 95% confidence intervals for the AUROC all overlapped with those of the ICH score alone. The highest discrimination was achieved when adding severe atrophy with an AUROC of 0.73 (95%CI 0.69-0.76).

Sensitivity analysis

In a sensitivity analysis using mRS>3 as the definition of poor functional outcome, the discrimination of the ICH score for mRS >3 was slightly better than for mRS >2 but the 95% confidence intervals overlapped (0.73 [95%CI 0.70-0.77] compared to 0.71 [95%CI 0.68-0.74], respectively; Table e-2).

Separate analyses for lobar and non-lobar ICH

We conducted separate analyses on lobar and non-lobar ICH separately (Table e-3A, e-3B, e-3C). This analysis confirmed the association between SVD biomarkers and outcome in both groups. In particular, in multivariable analysis cortical atrophy presence (OR 2.06 [95%CI 1.21-3.52]; p = 0.008), severe atrophy (OR 2.03 [95%CI 1.30-3.17]; p = 0.002) and severe SVD burden (OR 1.87 [95%CI 1.03-3.39]; p = 0.041) were strongly associated with outcome in non-lobar ICH (Table e-3D), while white matter hypodensities (OR 1.98 [95%CI 1.21-3.24]; p = 0.006), deep atrophy presence (OR 1.97 [95%CI 1.14-3.39]; p = 0.014) and severe white matter

hypodensities (OR 2.04 [95% CI 1.18-3.53]; p = 0.011) were associated with outcome in lobar ICH (Table e-3E). The revised oICH score performed slightly better in lobar ICH (AUC 0.72 [95%CI 0.67-0.77]), than in non-lobar ICH (AUC 0.69 [95%CI 0.65-0.73]) but with overlapping 95% CI. Adding SVD biomarkers to revised oICH score did not significantly improved outcome prediction of the oICH score alone (Table e-3F and e-3G). The best models for non-lobar ICH were obtained by adding cortical atrophy presence (AUC 0.71 [95%CI 0.66-0.75]) or severe atrophy presence (AUC 0.71 [95%CI 0.67-0.75]) to the score. For lobar ICH, the best model included the revised oICH score plus deep atrophy presence or oICH plus white matter hypodensities presence (in both models: AUC 0.74 [95%CI 0.69-0.79]).

DISCUSSION

Our study has confirmed acceptable discrimination and calibration for the prediction of 6-month functional outcome after ICH using a recalibrated version of the ICH score. We confirmed that some baseline CT biomarkers of SVD presence and severity are independently associated with 6-month functional outcome in univariable and multivariable models (adjusted for variables included in the ICH score). However, adding SVD biomarkers individually (or as a composite SVD burden score) did not lead to statistically significant improvement in the discriminative performance of the ICH score, regardless of ICH location.

Although many clinical-radiological scores have been developed, the ICH score remains widely used and validated, and performs well compared to others[5]. Four studies evaluated the performances of the ICH score for 6-months functional outcome prediction, and four studies for 12-months (pooled AUROC [0.78, 95% CI 0.74-0.82]; pooled AUROC 0.77 [95% CI 0.72-0.83], respectively). The discrimination of the ICH score in our study was not as high, although the

95% CI overlapped with that reported in previous studies. This might be due to differences in population characteristics and definitions of functional outcome. Previous studies included an Asian population [19], exclusively supratentorial ICH [20], or deep ICH with intraventricular extension[21]. Our population is likely to be more heterogeneous and therefore more generalizable to the full population of patients with ICH. We used mRS >2 to define poor functional outcome, but due to the severity of ICH, many studies use a cutoff of mRS>3; our sensitivity found that the discrimination of the ICH score for mRS >3 was slightly better than for mRS >2 (0.73 [95%CI 0.70-0.77] compared to 0.71 [95%CI 0.68-0.74], respectively). However, regardless of how poor outcome was defined, the addition of SVD biomarkers did not significantly improve predictive discrimination of ICH score alone.

Our findings that SVD markers are related to functional outcome suggest that SVD is an important factor in neurological recovery after ICH, in line with previous studies showing an association between baseline imaging features of SVD and cognitive impairment or functional outcome after ischemic and haemorrhagic stroke[22], [23]. The main reported associations are for 90-day outcome after ischemic stroke, and we are not aware of previous reports describing the impact of CT-based SVD markers on functional outcome beyond 3 months after ICH. Our results confirm previous data suggesting that WMH[10] and brain atrophy[24] are key factors through which SVD influences functional outcome. SVD could influence poor functional outcome via several mechanisms. First, SVD is likely to be associated with recurrent stroke after ICH; since most ICH are due to SVD, markers of its severity are likely to be associated with ICH recurrence risk. Second, SVD is associated with other vascular risk factors that could influence adverse vascular events. Third, SVD can lead to disruption of key brain networks likely to be

important for rehabilitation, learning, and cognitive reserve [25], which are important in determining functional recovery after ICH.

However, we found that adding CT markers to the ICH score did not increase ICH score predictive discrimination significantly. The optimal discrimination was obtained when adding severe atrophy to the revised ICH score, but this small improvement was not statistically significant. Our findings thus indicate that although CT biomarkers of SVD (using visual rating scales) are clearly relevant for understanding mechanisms of functional recovery after ICH, adding them to the ICH score is not likely to be helpful in clinical practice for predicting of 6-month outcome because it does not increase the predictive value of simple clinical-radiological characteristics of the index haemorrhagic event (age, ICH volume, location, intraventricular extension, conscious level). These findings were confirmed when considering lobar and non-lobar ICH separately; adding SVD biomarkers to the score did not significantly improve outcome prediction.

Our study measured functional outcome at a relatively early 6-month time point. Patients with acute ICH often have severe morbidity as a result of the haematoma, associated oedema, and intraventricular haemorrhage; these forms of brain injury seem to require a substantial time to resolve, meaning that functional improvement can occur beyond 6 months[26] [27] Thus, if SVD markers do influence ICH functional recovery, for example by impairing white matter connectivity (which might affect learning, general cognitive functioning, cognitive reserve and rehabilitation potential), they may not have additional influence over the initial ICH severity at the 6-month time-point, but could be a more important determinant of longer term outcome.

CT brain scanning is a standard of care for patients with acute ICH that is readily available in most stroke services worldwide. Thus, our findings are relevant for clinical services and future

research studies in large populations. Magnetic resonance imaging (MRI) has high sensitivity and specificity for detecting most manifestation of SVD[13], but is less accessible in many healthcare systems and is unsuitable for some patients (e.g. those who are unwell, claustrophobic, or have non-MRI compatible implants or devices). Nevertheless, further studies should assess the contribution of SVD markers assessed on MRI in improving outcome prognostication after ICH. Quantitative methods which can assess brain tissue microstructure and connectivity could be of particular interest; for example, diffusion tensor imaging techniques show promise for outcome prediction after both ischemic and hemorrhagic stroke[28], [29].

Our study has strengths. We evaluated a prospectively collected large cohort of ICH patients using a standardized protocol with good inter-rater agreement (with Cohen's kappa values comparable to previous studies). To the best of our knowledge this is the first attempt to improve outcome prognostication by adding CT-based markers of SVD to an existing clinical-radiological prognostic score. The visual rating methods we applied to quantify SVD burden on CT scans have been previously established[14] and can be applied to standard clinical CT scans that are usually part of standard clinical care. Given our multicenter design and large population cohort, with a range of ICH location and size, we expect that our results are generalizable, at least among the Western population. Our finding of lobar ICH in 41.8% of patients is consistent with previous population-based studies [30], suggesting that our cohort is generalizable to other ICH populations.

Our study also has limitations. The CROMIS-2 study required signed informed consent, which could have created a selection bias towards ICH survivors, limiting the inclusion of extremely severe ICH patients; this probably contributed to low rate of death at 6 months in our cohort.

However, data from the group of ICH patients who are likely to survive the acute phase is of most relevance to clinicians, patients and their families. Our findings also require validation in independent cohorts from other populations.

CONCLUSION

The ICH score demonstrated acceptable prognostication ability for 6-months functional outcome after spontaneous ICH. We found that CT-markers of SVD were associated with 6-month functional outcome when assessed independently in adjusted analyses, suggesting that they are relevant for ICH recovery mechanisms. However, adding them to the ICH score did not substantially improve predictive discrimination for 6-month functional outcome. Further studies investigating the influence of SVD markers on longer term outcome, and exploration of more advanced quantitative MRI methods are needed.

Table - Appendix 1 - Authors

Name	Location	Role	Contribution
Isabel C Hostettler	University College London	Author	Design of study; analysis and interpretation of data; drafting the manuscript for intellectual content.
Ghil Schwarz	University College London	Author	Design of the study; analysis and interpretation of data; drafting the manuscript for intellectual content
Gareth Ambler	University College London	Author	Analysis of data; revising manuscript for intellectual content
Duncan Wilson	University College London	Author	Analysis of data; revising manuscript for intellectual content
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Clare Shakeshaft	University College London	Author	Major role in acquisition of data; revising manuscript for intellectual content
Surabhika Lunawat	University College London	Author	Revising manuscript for intellectual content
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Hans Rolf Jäger	University College London	Author	Analysis of data; revising manuscript for intellectual content
Henry Houlden	University College London	Author	Revising manuscript for intellectual content
David J Werring	University College London	Author	Study conceptualisation and design; interpretation of data; revising manuscript for intellectual content

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Table 1. Baseline clinical characteristics, CT-based SVD biomarkers and outcomes

Variable	Patients included in analysis (N=864)
	N (%)
Age (mean)	73.6 (SD: 11.9)
Gender, female	362 (41.9)
Arterial Hypertension	580 (67.1)
Diabetes Mellitus	154 (17.8)
Atrial fibrillation	301 (34.8)
Hypercholesterolemia	371 (44.2)
Anticoagulant drug	345 (39.9)
Pre-ICH Cognitive Impairment§	70 (8.1)
Glasgow Coma Scale score (mean)	13.9 (SD: 1.9)
ICH Location:	
Deep	429 (49.6)
Lobar	361 (41.8)
Infratentorial	74 (8.6)
Intra-ventricular extension	256 (29.6)
ICH volume (mean)	14.9 (SD: 20.2)
White matter hypodensities	
Yes*	443 (51.3)
No	421 (48.7)
Severe white matter hypodensities	261 (30.2)
Lacunes	
Yes	91 (10.5)
No	773 (89.5)
Severe lacunes (lacunes ≥2)	18 (2%)
Deep atrophy	
None	225 (26.0)
Moderate	457 (52.9)
Severe	182 (21.1)

Cortical atrophy	
None	132 (15.3)
Moderate	573 (66.3)
Severe	159 (18.4)
Severe atrophy#	258 (29.9)
SVD burden score:	
Non-severe (0-1)	740 (85.7)
Severe (≥ 2)	124 (14.3)
Neurosurgery performed	26 (3.0)
Pre-ICH mRS (median; IQR)	0; 1
Pre-ICH mRS ≤ 2	745 (86.2)
mRS at 6 months:	
0	156 (18.0)
1	119 (13.8)
2	54 (6.3)
3	194 (22.5)
4	76 (8.8)
5	123 (14.2)
6	142 (16.4)

SD, Standard Deviation; ICH, intracerebral haemorrhage; SVD, small vessel disease; mRS, modified Rankin Scale

§ Pre-ICH cognitive impairment was considered present: (1) for those with a confirmed diagnosis of dementia prior to ICH, or (2) in case of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) > 3.3

**WMH present: if Van Swieten ≥1 (either anterior or posterior)*

 # Severe atrophy: if graded as severe in either deep or cortical regions

Table 2. Revised ICH score model. Multivariate analysis with calculation of β-coefficients and OR (and accordingly assigned integer score points) for original variables included in ICH score.

Variables	Points	β-coefficients	OR (95% CI)
GCS		1.24	3.44 (1.99-5.93)
*3 to 12	2		
13 to 15	0		
ICH Volume		1.26	3.54 (2.02-6.20)
≥30cc	2		
<30cc	0		
ICH Location		0.53	1.71 (1.00-2.91)
Infra-tentorial	1		
Supra-tentorial	0		
Age		1.10	3.02 (2.16-4.21)
≥ 80	2		
< 80	0		
IVH		0.57	1.77 (1.25-2.50)
Yes	1		
No	0		
	TOTA 0-8		

Score Interpretation

Points	Poor (mRS > 2) 6-months outcome rate
0	42%
1	56%
2	69%
3	80%
4	89%
5	94%
6	96%

7-8§	98%	

**only 5 patients in our cohort had a of GCS 3 or 4 (excluded);*
§ Only one patient with score 8;
GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intra-ventricular extension; WMH, white matter hypodensities; SVD, small vessel disease

Table 3. Clinical and radiological characteristics in the entire cohort and univariable associations with poor 6-month functional outcome (mRS >2)

	N (%)	Poor outcome (mRS >2)	OR (95% CI)	P value
Clinical Variables				
Age:			3.06 (2.22-4.22)	<0.001
>80	295 (34.1)	230 (78.0)		
<80	569 (65.9)	305 (53.6)		
GCS:				
3 to 4*	4 (0.4)	4 (100.0)		
5 to 12	130 (15.1)	112 (86.2)	4.7 (2.81-7.85)	<0.001
13 to 15	730 (84.5)	419 (57.4)		
ICH volume:			4.7 (2.76-7.99)	<0.001
<30	738 (85.4)	426 (57.7)		
≥30	126 (14.6)	109 (86.5)		
Intraventricular extension:			2.19 (1.59-3.03)	<0.001
Yes	256 (29.6)	190 (74.2)		
No	608 (70.4)	345 (56.7)		
Location:			1.31 (0.79-2.18)	0.296
Supratentorial	790 (91.4)	485 (61.4)		
Infratentorial	74 (8.6)	50 (67.6)		
CT SVD biomarkers				
White Matter Hypodensities			1.80 (1.36-2.37)	<0.001
Present	443 (51.3)	304 (68.6)		
Absent	421 (48.7)	231 (54.9)		
Lacunes:			1.09 (0.69-1.71)	0.706

Present	91 (10.5)	58 (63.7)		
Absent	773 (89.5)	477 (61.7)		
Severe WMH			1.48 (1.09-2.01)	
Yes	261 (30.2)	178 (68.2)		0.012
No	603 (69.8)	357 (59.2)		
Severe lacunes (lacunes≥ 2)			1.24 (0.46-3.32)	
Yes	18 (2.1)	12 (66.7)		0.675
No	846 (97.9)	523 (61.8)		
Cortical Atrophy:				
None	132 (15.3)	60 (45.5)		
Moderate	573 (66.3)	350 (61.1)	1.88(1.29-2.76)	0.001
Severe	159 (18.4)	125 (78.6)	4.41(2.65-7.35)	<0.001
Deep Atrophy:				
None	225 (26.0)	111 (49.3)		
Moderate	457 (52.9)	285 (62.4)	1.70 (1.23-2.35)	0.001
Severe	182 (21.1)	139 (76.4)	3.32 (2.16-5.11)	<0.001
Severe Atrophy:			2.36 (1.70-3.26)	
Yes	258 (29.9)	194 (75.2)		<0.001
No	606 (70.1)	341 (56.3)		
Severe SVD burden score:			1.84 (1.20-2.81)	
Non-Severe (0-1)	740 (85.6)	444 (60.0)		
Severe (2-3) §	124 (14.4)	91 (73.4)		0.004

** only 5 patients in our cohort had a GCS of 3 or 4 (excluded for OR evaluation)*

§ only 4 patients in our cohort with SVD score = 3 (excluded for OR evaluation)

AUROC, area under the curve; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intra-ventricular extension; WMH, white matter hypodensities; SVD, small vessel disease; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4. Association of SVD biomarkers and severe SVD burden score with poor functional outcome (mRS >2) at 6 months. *Models are adjusted for ICH score variables: age, GCS, ICH volume, Intraventricular extension, ICH location.*

	OR (95%CI)	P value
WMH presence	1.52 (1.12-2.06)	0.007
Lacunes presence	1.31(0.81-2.13)	0.268
Cortical atrophy presence	1.80 (1.19-2.73)	0.006
Deep atrophy presence	1.66 (1.17-2.34)	0.004
Severe WMH	1.29 (0.93-1.81)	0.132
Severe atrophy	1.94 (1.36-2.74)	<0.001
Severe SVD burden score	1.57 (0.99-2.48)	0.053

GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intra-ventricular extension; WMH, white matter hypodensities; SVD, small vessel disease; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5. Sequential addition to ICH score of dichotomized CT-based markers of SVD significantly related to outcome.

			New Model		
			ICH score + single CT marker		
			Points added	**AUROC**	**HL p value**
			for CT variable	(95% CI)	
ICH score	+	**WMH**		0.72	0.30
		Present	1	(0.68-0.75)	
		Absent	0		
ICH score	+	**Cortical atrophy**		0.72	0.71
		Present	1	(0.68-0.75)	
		Absent	0		
ICH score	+	**Deep atrophy**		0.72	0.69
		Present	1	(0.68-0.75)	
		Absent	0		
ICH score	+	**Severe atrophy**		0.73	0.96
		Present	1	(0.69-0.76)	
		Absent	0		
ICH score	+	**SVD burden score**		0.72	0.41
		Severe (0-1)	1	(0.68-0.75)	
		Non-severe (2-3)	0		

AUROC area under the receiver operating characteristic; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intra-ventricular extension; WMH, white matter hypodensities; SVD, small vessel disease; HL, Hosmer-Lemeshow test.