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# **Do Clinicians Overestimate the Severity of Intracerebral Hemorrhage?**

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Tables 1; Figures 4

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## **Abstract**

**Background and Purpose:** Intracerebral Hemorrhage (ICH) has a poorer prognosis than acute ischemic stroke (AIS). However, clinician perception of prognosis may influence treatment decisions and adversely affect outcome. On acute CT, the conspicuity of ICH compared to AIS may lead clinicians to overestimate severity and influence prognostic evaluation. We investigated whether clinicians' estimates of volume, severity and prognosis from acute imaging differed between ICH and AIS.

**Methods:** CT scans from participants with acute ICH or ischemic stroke were reviewed. Volume was calculated using the ABC/2 method and automated volumetric analysis via specialised imaging software. ICH cases were matched with AIS cases for lesion volume, based on acute (<6h) CT for ICH, and 24h CT for AIS. Blind to clinical information, clinicians estimated lesion volume to the nearest 5ml, graded lesion severity from 1 (mild) to 5 (very severe) and estimated 30-day prognosis using the modified Rankin Scale (mRS).

**Results:** We compared 33 ICH cases with 33 volume-matched AIS cases. Clinicians overestimated ICH volume and underestimated AIS volumes: mean differences (estimated - actual volume) were +8ml ( $\pm 30$ ) for ICH and -8ml ( $\pm 27$ ) for AIS ( $p < 0.001$ ). Observers rated ICH to be of greater severity and poorer prognosis compared to AIS cases: 109/265 [41%] ICH cases rated severity categories 4 or 5 compared to 36/257 [14%] AIS,  $p < 0.001$ ; estimated mRS 0-2 in 125/265 [47%] of ICH compared to 190/257 [74%] AIS,  $p < 0.001$ . Results were unaffected by presence of intraventricular blood. Estimated severity and prognosis for ICH remained significantly worse compared to AIS after adjustment for estimated volumes.

**Conclusions:** Clinicians overestimated ICH volume and severity compared to AIS of equivalent volume, and also assigned significantly worse prognosis independent of volume estimates.

## **Background**

Intracerebral hemorrhage (ICH) has a poorer prognosis than acute ischemic stroke (AIS). One month mortality following ICH is estimated to be approximately 40%, around four times that seen in AIS [1-3]. Long term outcomes are comparably poor: survival following ICH is 46% at one year, with 75% either deceased or severely disabled [4].

A negative perception of prognosis may, however, impact significantly on the management of patients with ICH. Clinical underestimation of the chances of favorable outcome in severe ICH cases may prompt clinicians to limit intensive management strategies [5, 6] and lead to early implementation of end-of-life protocols, with the inevitable consequence of higher mortality among these patients [7]. Prognosis may therefore be biased as a consequence of clinical perception. However, Clinician assessment of prognosis has been shown to more closely predict 3-month outcome ICH than prognostic scales [8].

Despite the differences in outcomes between ICH and AIS, previous studies have reported that stroke type did not influence prognosis when lesion volume and initial severity of symptoms were accounted for [9]. Greater average lesion volume in ICH compared to AIS may determine greater stroke severity in ICH, and thus prognosis [10]. More recent registry data reinforce the average greater severity of ICH compared to AIS and suggest association

of poorer prognosis to be independent of stroke type [11]. However, these comparisons may be similarly confounded by potential clinical bias in management strategies.

We hypothesized that clinicians would exhibit negative perceptions of ICH compared to AIS by over-estimating the volume of brain lesions, assigning greater clinical severity and predicting poorer outcome based on acute CT appearances.

## **Methods**

### **Study Design and Participants:**

This was a single center, retrospective, case-control study. Anonymized CT scans were selected from a local database of scans obtained from participants in observational or interventional research studies, where acute imaging was obtained. ICH cases presented between July 2013 and September 2016 and AIS cases between January 2009 and September 2013. Oral anticoagulant-associated ICH cases were excluded. Ethical approval for the studies was given by national ethics committees and included participant consent for further imaging based research using de-identified scans. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### **Group Characteristics:**

Clinical, demographic and stroke presentation characteristics were recorded for each participant. These included age, sex, past medical history and admission National Institute of Health Stroke Scale (NIHSS) and estimated pre-stroke modified Rankin Scale (mRS) scores [12, 13].

**Image Analysis:**

Whole brain non-contrast CT scans were acquired using either a Philips Brilliance 64 slice scanner, (120kV, slice thickness 0.6mm) or a General Electric optima scanner (120kV, slice thickness 0.6mm). Scans for the ICH cases were acquired <6h after onset of symptoms. AIS cases were also recruited <6h after symptom onset but follow-up imaging carried out at approximately 24 hours was used for comparison in this study to ensure sufficient time had passed to allow adequate visualization of the final infarct. Scans were reviewed for presence or absence of intraventricular extension and ICH location (lobar or deep). ICH volumes were calculated by two techniques; the ABC/2 method [14, 15] using manual measurement of maximal ICH diameter in three perpendicular x, y and z planes on a 5mm thick slice of a multi-planar whole brain non-contrast CT image. Since the ABC/2 method assumes approximately ovoid geometry and may not estimate volume of irregularly shaped ICH accurately, we additionally undertook volumetric analysis using the imaging package MISTar (version 3.2.63) by manually placing a seed region of interest (ROI) in the hemorrhage on a single axial 5mm slice, followed by growing the ROI using automated thresholding then summation of multiple axial frames to derive a volume.

For each scan, a single observer calculated lesion volumes twice, with a minimum interval of two weeks between the first and second measurements. The observer was blinded to first measurements at the time of second measurement. The mean of the two measurements was used as the lesion volume. Each of the ICH cases was matched with an AIS scan selected to be within  $\pm 10\%$  of the volume of the ICH scan. Infarct volumes for the AIS comparators had been previously calculated using the same MISTar imaging package.

**Scan Review:**

Scans were presented with no accompanying clinical information in a random order to clinicians of different levels of experience. Participants were asked to 1) estimate lesion volume to the nearest 5ml; 2) give a subjective impression of expected clinical severity on a scale of 1-5 (1 = mild, 5 = very severe); and 3) estimate 30-day prognosis by mRS (0-6).

### **Statistical Analysis:**

Statistical analyses were performed using IBM SPSS Statistics version 21.0. Categorical variables are presented as frequencies and proportions and were compared using Pearson  $\chi^2$  test for association and Fisher's Exact tests. Continuous variables are described as either mean ( $\pm$ standard deviation [SD]), or median (interquartile range [IQR]) and compared using independent samples t-test or Mann Whitney U tests for normally and non-normally distributed data respectively. Binary logistic regression analysis was carried out to assess factors (including stroke type, lesion volume, observer experience, patient age) predicting estimated favorable prognostic outcome (defined by mRS 0-2).

## **Results**

### **Study participants and cohort characteristics**

Thirty-three CT scans were obtained for analysis as the ICH group, and were matched to 33 AIS comparator CT scans from a local research imaging database. Comparison of clinical characteristics for the two groups (Table 1) showed higher median National Institutes of Health Stroke Scale (NIHSS) scores in the ICH group (17, IQR 10-21) compared to the AIS group (9, IQR 5-14,  $p=0.002$ ). The level of consciousness component (NIHSS item 1a) was zero in most cases in both groups (19/33 ICH and 28/33 AIS). Atrial fibrillation ( $p=0.002$ ) and hyperlipidemia ( $p=0.039$ ) were more prevalent in the AIS group.

**Scan review:**

A median of 8 (IQR 8-8.25) observers reviewed each scan. Forty-eight percent (n=16) of observers were experienced (14 stroke physicians, 2 neurologists) and 17 less experienced (5 senior medical trainees, 7 junior medical trainees, 4 clinical research fellows, 1 stroke research nurse specialist).

A median of 6 (IQR 5-7) volume estimations were made per scan. Thirteen scans from both the ICH and the AIS groups had  $\leq 5$  volume estimates. Mean measured lesion volume was the same for both groups:  $25 \pm 30$  ml for the ICH group and  $26 \pm 32$  ml for the AIS group (Figure 1). Mean estimated lesion volume for ICH cases was significantly greater than for AIS cases ( $32 \pm 33$ ml compared to  $17 \pm 23$ ml respectively,  $p < 0.001$ ). The mean difference between estimated and actual lesion volume was  $+8$ ml ( $\pm 30$ ) for the ICH group and  $-8$ ml ( $\pm 27$ ) for the AIS group ( $p < 0.001$ , Figure 2). A sensitivity analysis found that there was no difference in volumes between scans that had  $\leq 5$  volume estimates when compared to scans with  $> 5$ .

There were 265 estimates of clinical severity and 30-day prognosis for the ICH group and 257 for the AIS group. Clinicians graded ICH to be of greater severity than AIS (Figure 3) with estimates of greatest severity (categories 4 or 5) in 41% (n=109) of ICH case estimates compared to 14% (n=36) for AIS cases ( $p < 0.001$ ). Clinicians also estimated ICH cases to have less likelihood of favorable 30-day prognosis (defined as mRS 0-2) predicting independent recovery in 47% (n=125) of ICH cases compared to 74% (n=190) of AIS cases (Figure 4,  $p < 0.001$ ). Differences remained statistically significant for both analyses after omitting observers who did not make volume estimations.



In binary logistic regression, significant univariate predictors of estimated favorable outcome (mRS 0-2) were stroke type (ICH compared to AIS, odds ratio 0.31, 95% confidence interval 0.19 - 0.48,  $p < 0.001$ ) and estimated lesion volume (odds ratio 0.56, 95% CI: 0.49 - 0.65,  $p < 0.001$ ). Observer experience (experienced compared to less experienced observers (odds ratio 1.83, 95% CI: 0.89 - 2.12,  $p = 0.145$ ) and patient age (odds ratio 1.07, 95% CI: 0.90 - 1.29,  $p = 0.443$ ) were not. In multivariable logistic regression, predicted favorable outcome remained significantly associated with stroke type (odds ratio for ICH 0.47, 95% CI: 0.28 - 0.80,  $p = 0.005$ ) after adjusting for estimated lesion volume.

In exploratory analyses, we assessed whether radiological features that might have influenced observers modified the association of stroke type with estimated prognosis. Intraventricular hemorrhage (IVH) was present in 11 of 33 ICH cases (33%) but did not significantly influence estimated lesion volume or predicted outcome. Differences in volume estimations between AIS and ICH groups remained statistically significant after excluding cases with IVH. Presence of IVH was unrelated to either actual or estimated parenchymal ICH volumes: Comparing presence and absence of IVH cases, measured parenchymal ICH volumes were 22ml and 27ml respectively ( $p = 0.174$ ) and estimated ICH volumes 30ml and 34ml ( $p = 0.498$ ). Forty-three percent ( $n = 31$ ) of IVH positive cases were predicted to have mRS 0-2 compared to 48% ( $n = 93$ ) of IVH negative cases ( $p = 0.480$ ). Median midline shift was 2.5mm in both ICH and AIS groups (Mann-Whitney U-test,  $p = 0.658$ ). Ventricular effacement of any degree was more commonly seen in ICH cases 19/33 cases versus 10/33, odds ratio 3.12, 95% CI 1.13-8.60). Both midline shift and ventricular effacement were each associated with poorer estimated mRS outcomes. In a logistic regression analysis that included midline shift and ventricular effacement, stroke type remained significantly associated with reduced odds of favorable estimated 30 day mRS (OR 0.44, 95% CI 0.29-0.67,  $p < 0.001$ ).

There were 13 deep / basal ganglionic and 20 lobar ICH cases. Deep/ basal ganglionic ICHs were smaller than lobar ICH (17ml compared to 36ml,  $p<0.001$ ). Estimated lesion volumes for both deep/basal ganglionic bleeds and lobar bleeds were significantly greater than measured volumes (22ml and 46ml respectively,  $p<0.001$  for each). Sixty percent ( $n=86$ ) of deep/basal ganglionic bleeds were estimated to have a favorable 30 day prognosis compared to 31% ( $n=38$ ) of lobar ICH cases ( $p<0.001$ ).

## **Discussion**

Using CT scans matched for lesion volume, we found that clinicians significantly overestimated the volume of ICH, and underestimated the volume of AIS. In addition, clinicians estimated clinical severity to be significantly greater for ICH, and predicted less likelihood of favorable day 30 outcomes for ICH compared to AIS, even after adjusting for estimated lesion volume, and independent of radiological features including midline shift, and ventricular effacement.

Intraventricular hemorrhage is associated with greater ICH severity [16-18], and was present in a third of our ICH cases but did not appear to influence clinicians' interpretation of volume, severity or prognosis.

Limitations of this study include its small sample size and its single center, retrospective design. We did not match cases for imaging features denoting "brain frailty", such as the presence of brain atrophy, established cerebrovascular lesions or small vessel disease [19, 20] that may have impacted clinicians' estimates; however, patient age (as a surrogate for brain

frailty measures) did not modify the significant differences between ICH and AIS in estimated prognosis. While we selected control cases on the basis of lesion volume, location may also be relevant to both prognosis and severity, and was not matched across the study groups [21, 22]. Similarly, we were not able to account for other factors of prognostic relevance such as hematoma location, intraventricular hemorrhage, hematoma density and morphology, [23-27] which often have no correlate in AIS cases. Additionally, a single baseline CT cannot capture the dynamic nature of ICH, the hematoma expansion commonly seen in the early hours after onset signifying poorer prognosis [28-30].

A greater propensity for deep location of ICH compared to AIS with internal capsular involvement could have accounted for the higher median NIHSS scores in ICH cases, since motor function represents a higher proportion of scores than other aspects of neurological deficit [12]. Level of consciousness accounted for only a small proportion of total NIHSS score in both groups. It is possible that observers may have taken lesion location into account when making prognostic estimations, but this could not be included in our analysis since the inherently different pathologies make matching of both volume and location for ICH cases with equivalent AIS cases extremely challenging. Lobar hemorrhages were estimated to have poorer 30-day prognosis compared to deep/basal ganglionic ICH, but lobar ICHs were significantly larger, therefore volume is likely to be the dominant factor considered by clinicians.

Our results suggest that a bias is present among clinicians in assessing stroke severity and prognosis for ICH compared to AIS. This may be of importance since outcomes are significantly affected by acute management, including end-of-life decisions or delays in secondary preventative treatment or rehabilitation [31-33].

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None

## Conflicts of Interest/ Disclosures

On behalf of all authors involved there are no conflicts of interest or disclosures

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## Figure Legends

*Table 1: Cohort characteristics for study participants according to stroke type.* AIS denotes acute ischemic stroke, ICH intracerebral hemorrhage, SD standard deviation, NIHSS National Institutes of Health Stroke Scale, IQR interquartile range, mRS modified Rankin Scale, TIA transient ischemic attack

*Figure 1: Scatter plot showing actual against estimated lesion volume for acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH) cases.* Each point represents an individual case. Solid lines represent the line of best fit for average estimation for a given volume. Dotted lines represent 95% confidence intervals for average estimation for a given volume.

*Figure 2: Individual value plot highlighting difference between estimated and actual lesion volumes for the acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH) cases.* Each point represents an individual case.

*Figure 3: Stacked bar chart illustrating distribution of severity estimations for acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH) cases.* Figures in each category denote n (%).

*Figure 4: Stacked bar chart illustrating distribution of 30-day prognosis estimations on the modified Rankin Scale (mRS) for acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH).* Figures in each category denote n (%).

## Tables

*Table 1: Cohort characteristics for study participants according to stroke type*

Characteristics	AIS participants (n=33)	ICH participants (n=33)	P value
Lesion Volume (ml), Mean (±SD)	26 (±31.9)	25 (±30.2)	0.885*
Age (years), Mean (±SD)	66 (54-78)	69 (55-83)	0.409*
Male sex, n (%)	23 (70%)	19 (58%)	0.443†
Smoker, n (%)	14 (42%)	13 (39%)	1.00†
Baseline NIHSS, Median (IQR)	9 (5-14)	17 (10-21)	0.002‡
Underwent thrombolytic treatment, n (%)	31 (94%)	0 (0%)	<0.001†
Pre-stroke mRS			
0	29 (88%)	25 (76%)	
1	1 (3%)	1 (3%)	
2	1 (3%)	3 (9%)	
3	1 (3%)	4 (12%)	0.379§
>3	0 (0%)	0 (0%)	
Not Provided	1 (3%)	0 (0%)	
Past Medical History			
Hypertension, n (%)	16 (48%)	21 (64%)	0.321†
Diabetes Mellitus, n (%)	5 (15%)	6 (18%)	1.00†
Ischemic heart disease, n (%)	6 (18%)	4 (12%)	0.144§
Atrial Fibrillation, n (%)	9 (27%)	0 (0%)	0.002†
Hyperlipidemia, n (%)	16 (48.5%)	7 (21%)	0.039†
AIS or TIA, n (%)	4 (12%)	4 (12%)	1.00§
Antiplatelet therapy, n (%)	14 (42%)	9 (27%)	0.301†

Statistical Tests: \* 2-sample t-test, † Chi-squared test of association with continuity correction, ‡ Mann Whitney test, § Fisher's exact test

## Figures

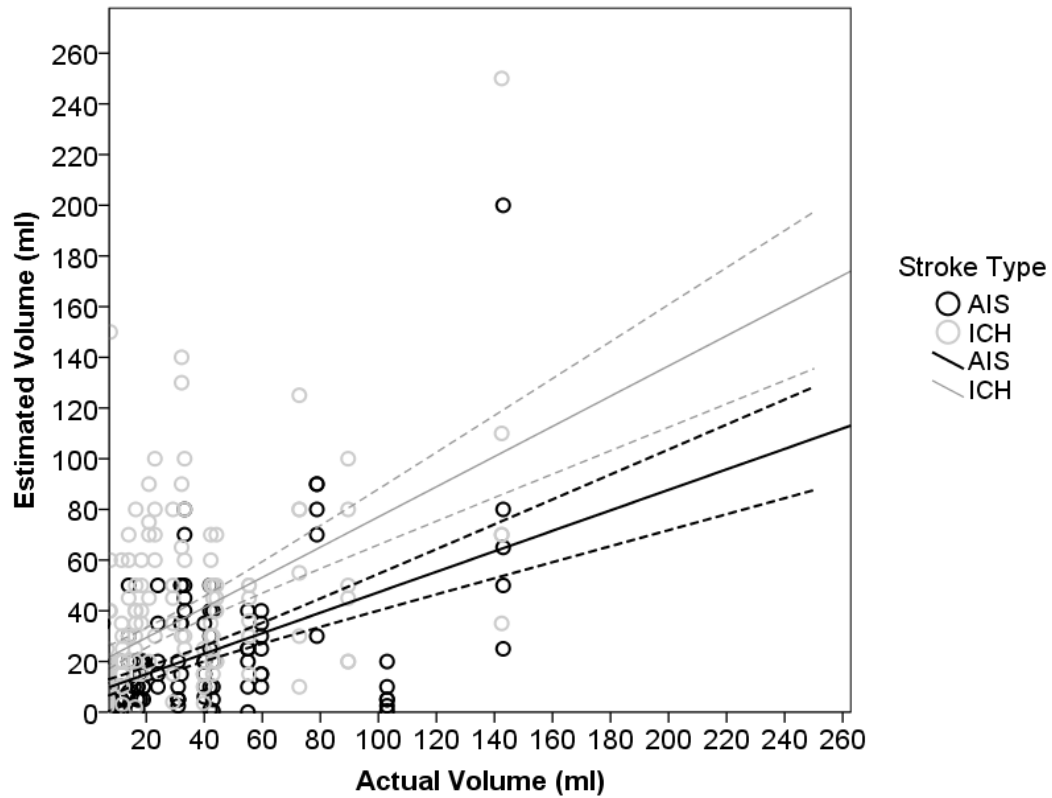


Figure 1: Actual against estimated lesion volume for AIS and ICH

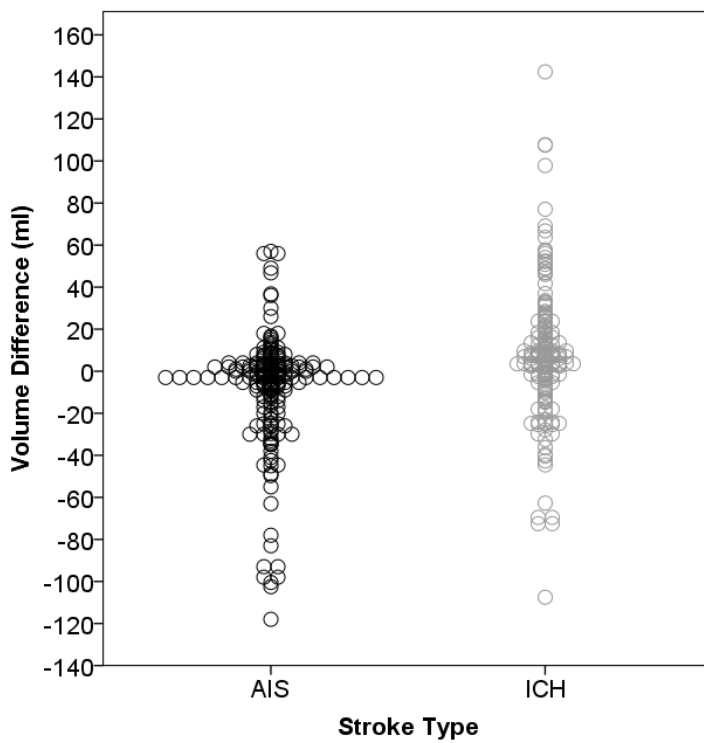


Figure 2: Difference between estimated and actual lesion volumes for AIS and ICH

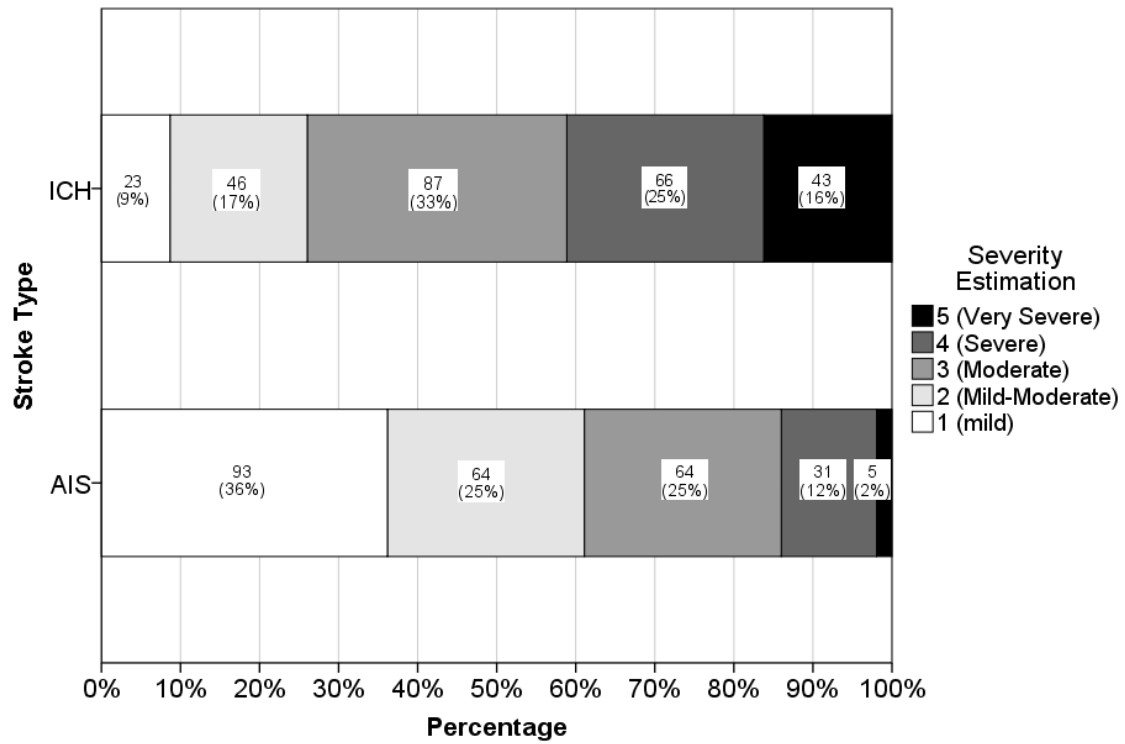


Figure 3: Distribution of severity estimations for AIS and ICH

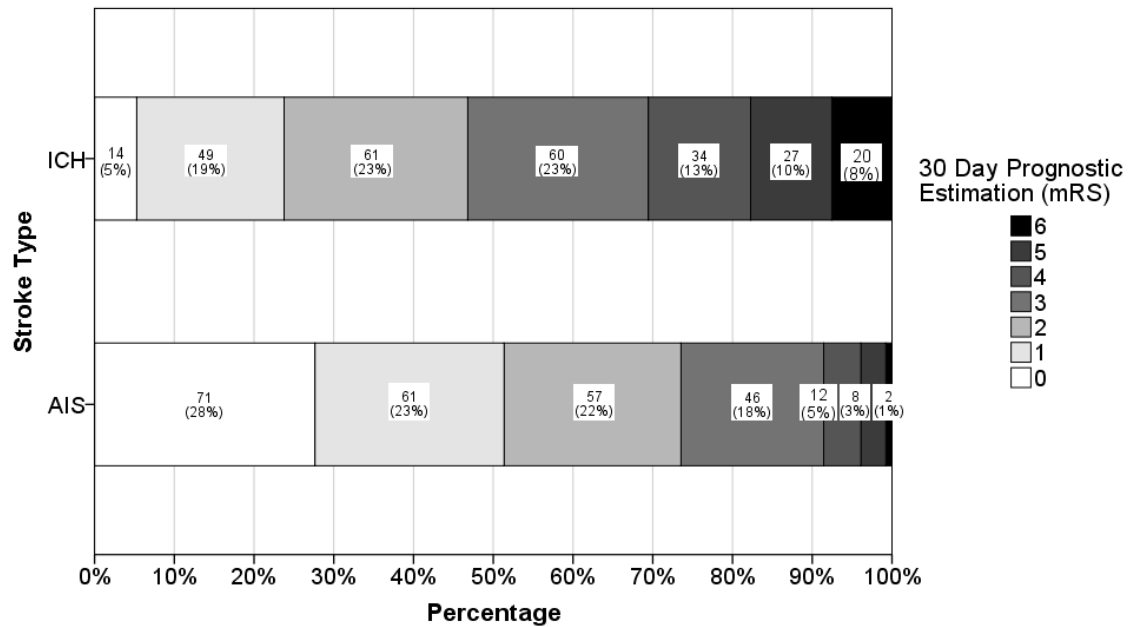


Figure 4: Distribution of 30-day prognostic estimations on the mRS for AIS and ICH