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# Location-Specific Hematoma Volume Cutoffs Predicting Three-Month Functional Outcome in Acute Primary Intracerebral Hemorrhage: A Prospective Observational Study From Bangladesh

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## Abstract

### Background

Hematoma volume is the strongest imaging predictor of outcome after intracerebral hemorrhage, but it is usually judged against one global threshold that ignores how differently each intracranial compartment tolerates blood. Location-specific thresholds derived in East Asian and North American cohorts have never been tested in South Asia.

### Methods

We conducted a prospective observational study of 120 conservatively managed adults with acute primary intracerebral hemorrhage at Dhaka Medical College Hospital between March 2024 and August 2025, enrolling 30 patients each for lobar, deep, cerebellar, and brainstem hemorrhage. Volume was measured on the admission non-contrast computed tomography scan using the ABC/2 method multiplied by slice thickness. Outcome was assessed with the modified Rankin Scale at three months and dichotomized into good, a score of 0-3, and poor, a score of 4-6. Receiver operating characteristic curves were built for each location; the cutoff with the highest Youden index was selected, and logistic regression tested whether the association persisted after adjustment for location. Classification performance was corrected for optimism with 2000 bootstrap samples, and location-specific thresholds reported by three earlier cohorts from East Asia and North America were applied unchanged to our patients for comparison. A sensitivity analysis excluded lobar hemorrhage, for which no valid cutoff was found.

### Results

At three months, 89 patients (74.2%) had a good outcome, 31 (25.8%) had a poor outcome, and 12 (10.0%) died. Median volume was 5.0 mL with a good outcome and 10.0 mL with a poor outcome ($p = 0.004$). Discrimination was excellent for brainstem hemorrhage, area under the curve 0.894 with a cutoff of 2.9 mL, and for cerebellar hemorrhage, 0.889 with a cutoff of 6.1 mL. It was moderate for deep hemorrhage, 0.691 with a cutoff of 9.8 mL, and absent for lobar hemorrhage, 0.388, for which no reliable cutoff could be derived. Classifying patients against the threshold for their own location gave a sensitivity of 74.2%, a specificity of 82.0%, and an accuracy of 80.0%, compared with 83.9%, 49.4%, and 58.3%, respectively, for a single cutoff of 3.9 mL (McNemar $p < 0.001$). After excluding lobar hemorrhage, accuracy was 77.8% against 65.6% for the single cutoff (McNemar $p = 0.013$). After bootstrap correction for optimism, the accuracy was 76.2%. Applied to our patients, the only published set covering all four locations gave an accuracy of 65.8%, against 80.0% for our thresholds, and a second set detected only four of 20 poor outcomes. A hematoma at or above the threshold for its location remained associated with a poor outcome after adjustment for location (odds ratio 19.87, 95% CI 5.66-69.81, $p < 0.001$).

### Conclusions

In conservatively managed patients, the volume that predicts a poor three-month outcome differs by more than an order of magnitude across intracranial locations. Thresholds of 2.9 mL for the brainstem and 6.1 mL for the cerebellum identified patients at risk accurately and outperformed a single global cutoff, whereas no reliable threshold could be derived for lobar hemorrhage. Where the admission computed tomography scan is the main prognostic tool, location-specific thresholds may improve on total volume alone, but because they rest on only 5 to 11 poor outcomes per location, they are exploratory and require external validation

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before they are used to guide clinical decisions.

**Categories:** Neurology, Radiology, Epidemiology/Public Health
**Keywords:** bangladesh, hematoma volume, intracerebral hemorrhage, modified rankin scale, prognosis, receiver operating characteristic curve

## Introduction

Intracerebral hemorrhage is the most lethal form of stroke. It accounts for roughly one in five strokes worldwide, yet it contributes a far larger share of stroke deaths and of years lived with disability [1,2]. A recent systematic review found that one-month case fatality has hardly changed over three decades and remains close to 40%, and that fewer than one-third of survivors regain functional independence [1]. The burden falls hardest on low- and middle-income countries, where case fatality is higher and access to neurocritical care is limited [1,3]. In Bangladesh, a nationwide survey estimated a stroke prevalence of 11.39 per 1000 population, of which 15.7% were hemorrhagic [4], and hospital-based series from the country continue to report 30-day mortality of more than 40% [5].

Against this background, prognostication is not an academic exercise. In most Bangladeshi hospitals, the decision to admit a patient to a high dependency bed, to seek an urgent neurosurgical opinion, to counsel a family about the realistic ceiling of recovery, or to commit scarce rehabilitation resources is taken within hours of arrival, and it rests on one noncontrast computed tomography scan and a bedside neurological examination. Advanced imaging, continuous invasive monitoring, and rapid access to surgery are rarely available. Current guidance on neuroprognostication acknowledges that predictions made in this early window carry substantial uncertainty and can become self-fulfilling when they prompt early limitation of treatment [6]. Anything that sharpens the earliest estimate of outcome has immediate clinical value.

Hematoma volume is the strongest single imaging predictor of outcome after intracerebral hemorrhage, and it can be obtained at the bedside from the admission scan using the ABC/2 method [7,8]. In everyday practice, however, volume is interpreted against one global threshold, most often the 30 mL boundary embedded in the original intracerebral hemorrhage score [7]. That practice is biologically implausible. The intracranial compartments differ profoundly in compliance, and in the density of eloquent tissue they contain. A 3 mL hematoma in the pons interrupts long tracts and compresses the reticular formation, while a hematoma ten times larger in a frontal lobe may leave a patient walking. Treating these two events as equivalent blunts prognostication, and probably blunts clinical trials as well, because it pools patients whose expected trajectories are entirely different [9].

Three cohorts have shown that location-specific thresholds outperform a single global cutoff. Leasure and colleagues derived and validated cutoffs of 8 mL for thalamic and 18 mL for basal ganglia hemorrhage [10]. Ironside and colleagues reported thresholds of 21.0 mL for lobar, 7.0 mL for deep, 12.0 mL for cerebellar, and 2.0 mL for brainstem hemorrhage for functional dependence at 90 days [11]. Teo and colleagues, working in a Hong Kong stroke registry, described cutoffs for a good six-month outcome that ranged from 3 mL for the brainstem to 40.5 mL for lobar hemorrhage, with higher cutoffs for a poor outcome, and showed that almost all of these models discriminated well [9]. All three cohorts were East Asian or North American. They differ from South Asian populations in age structure, hypertension control, anticoagulant exposure, and availability of surgery, so their numbers cannot simply be borrowed. Studies of intracerebral hemorrhage from Bangladesh remain few, and none of them have reported outcome thresholds separately for each hemorrhage location [5,12,13].

We therefore carried out a prospective study of conservatively managed patients with acute primary intracerebral hemorrhage to determine, for lobar, deep, cerebellar, and brainstem hemorrhage separately, the admission hematoma volume that best predicts a poor functional outcome at three months, to measure how accurately those thresholds perform, and to compare them with a single global threshold and with previously published location-specific thresholds.

## Materials And Methods

### Study design and setting

This prospective observational study was carried out in the Department of Neurology, Dhaka Medical College Hospital, Dhaka, Bangladesh, over an 18-month period from March 2024 to August 2025.

### Participants

Adults older than 18 years admitted with acute primary intracerebral hemorrhage confirmed on non-contrast computed tomography of the head were screened. Primary intracerebral hemorrhage was defined as bleeding caused by rupture of small intracranial vessels damaged by small vessel disease, occurring without head trauma and without a visible structural cause such as a vascular malformation, a saccular aneurysm, or a hemorrhage-prone neoplasm [14]. Stroke was defined according to the accepted international definition

[15]. Patients were included if they were older than 18 years, had acute primary intracerebral hemorrhage confined to a single location (lobar, deep, cerebellar or brainstem) on the admission scan, were managed conservatively without neurosurgical intervention, and gave written informed consent personally or through a legally authorized representative.

Patients were excluded if the hemorrhage was secondary to trauma, a brain tumor, or a coagulopathy; if there was hemorrhagic transformation of an infarct on computed tomography or magnetic resonance imaging; if they underwent any neurosurgical intervention; if the hematoma involved more than one location; if there was a recurrent stroke within six months of the index event; if there was subarachnoid hemorrhage; if computed tomography angiography or digital subtraction angiography demonstrated an arteriovenous malformation or an aneurysm; or if they were lost to follow-up at three months.

## Sample size and sampling

The sample size was initially planned using the formula described by Buderer for estimating sensitivity [16]:

$$
n = \frac{Z^{2} \times Se \times (1-Se)}{d^{2} \times P}
$$

where $n$ is the required sample size, $Z$ is the standard normal deviate corresponding to a two-sided 5% level of significance (Z=1.96), $Se$ is the expected sensitivity, $d$ is the acceptable absolute error, and $P$ is the prevalence of the target condition, defined in this study as poor functional outcome.

An expected sensitivity of 96% (Se=0.96) was obtained from the largest previous location-specific study [9]. The acceptable error was set at 10% of the expected sensitivity:

$$
d = 0.10 \times 0.96 = 0.096
$$

Accordingly, the number of patients with a poor functional outcome required for estimating sensitivity at each hemorrhage location was calculated as:

$$
\frac{1.96^{2} \times 0.96 \times 0.04}{0.096^{2}} = 16.0
$$

Thus, approximately 16 patients with a poor functional outcome were required at each hemorrhage location.

At the protocol stage, the prevalence of deep intracerebral hemorrhage, 55.6% (P=0.556), was entered into the formula. The calculated sample size was therefore:

$$
n = \frac{1.96^{2} \times 0.96 \times 0.04}{0.096^{2} \times 0.556} = 28.8
$$

This value was rounded up to 29 patients per hemorrhage location. However, the value of 55.6% represents the frequency of a hemorrhage location rather than the prevalence of the target outcome being predicted. Therefore, its use as $P$ does not provide a statistically valid justification for the calculated sample size.

Based on the observed prevalence of poor functional outcome in the present cohort, 25.8% (P=0.258), the same formula would yield:

$$
n = \frac{1.96^{2} \times 0.96 \times 0.04}{0.096^{2} \times 0.258} \approx 62.0
$$

Thus, approximately 62 patients would be required for each hemorrhage location, corresponding to a total sample size of:

$$
N = 62 \times 4 = 248
$$

Because the actual study included only 5 to 11 patients with poor functional outcomes within each hemorrhage location, the location-specific diagnostic accuracy analyses should therefore be considered

exploratory.

A non-randomized purposive sampling strategy was used, and 30 patients were enrolled from each of the four hemorrhage locations, resulting in a total sample size of:

$$
N = 30 \times 4 = 120
$$

This approach was adopted because cerebellar and brainstem hemorrhages are substantially less frequent than deep and lobar hemorrhages [3]. Consequently, consecutive enrollment of all eligible admissions throughout the study period would likely have yielded an insufficient number of posterior fossa hemorrhages to construct separate receiver operating characteristic curves for each anatomical location.

A quota of 30 patients per hemorrhage location was therefore prespecified at the protocol stage so that each of the four locations contributed an equal number of patients to its respective analysis. However, given the limitation in the original sample size calculation described above, this quota should be regarded as a pragmatic sampling decision rather than a statistically justified sample size.

During the study period, admitted patients were screened according to the predefined eligibility criteria. Eligible patients were enrolled in the order of admission until the quota of 30 patients for their respective hemorrhage location was reached. As completion of the three-month functional outcome assessment was required for inclusion in the final analysis, only patients with complete three-month follow-up data were analyzed. The overall participant selection process is summarized in Figure *1*.

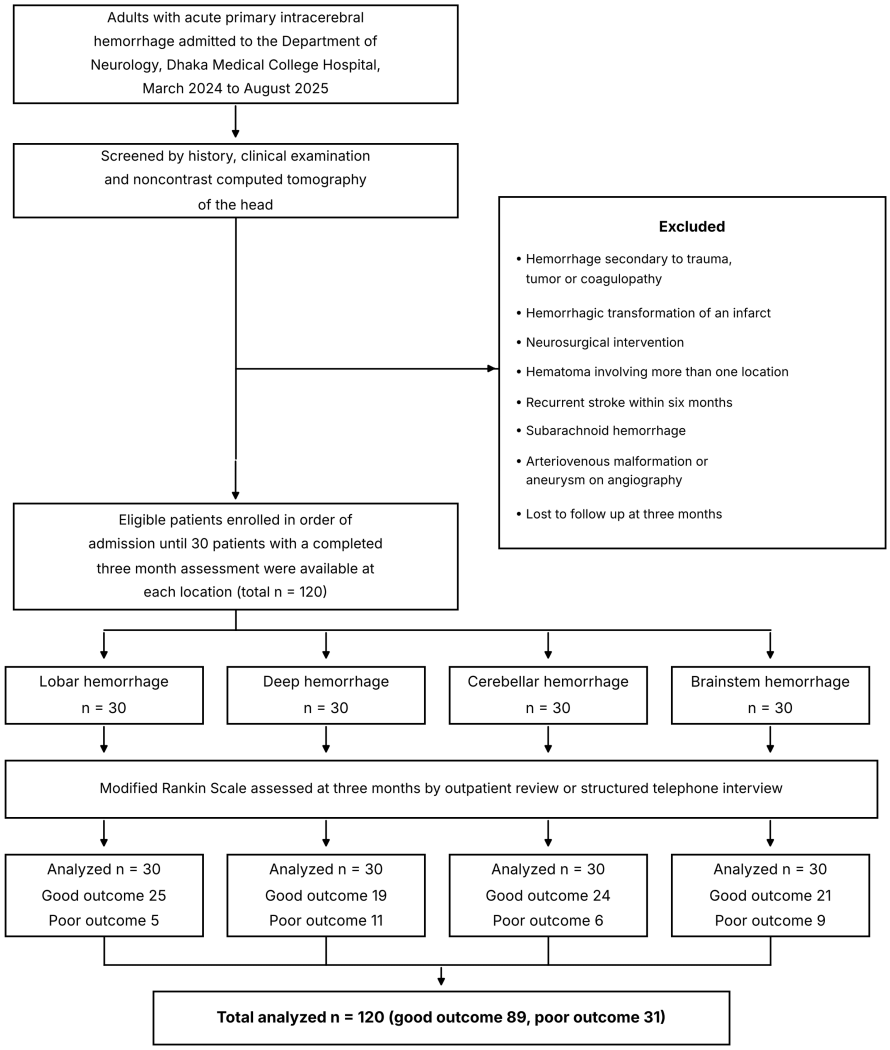



**FIGURE 1: Flow diagram of patient selection, enrollment and analysis at each hemorrhage location**

## Data collection

A structured case record form was completed by the investigator from the patient or, when the patient could not respond, from a close attendant. It captured age, sex, residence, education, occupation, monthly income, personal history of smoking, alcohol consumption and substance abuse, comorbid conditions, presenting complaints, the interval from symptom onset to imaging, admission pulse and blood pressure, the Glasgow Coma Scale [17], the National Institutes of Health Stroke Scale [18] and the intracerebral hemorrhage score [7]. All of these instruments, together with the modified Rankin Scale, are freely available for clinical and research use, and no permission was required for their use in this study.

## Imaging and hematoma volume measurement

All scans were performed on a 128-slice computed tomography scanner and were reviewed jointly with the Department of Radiology and Imaging. Hematoma location was assigned according to the site in which the hematoma originated, following the definitions used in previous location-specific studies [9,11]. Lobar hemorrhage was defined as a hematoma originating in the cortex or the cortical subcortical junction of the frontal, parietal, temporal, or occipital lobe. Deep hemorrhage was defined as a hematoma involving the thalamus or the basal ganglia, including the putamen, the globus pallidus and the internal and external capsules. Cerebellar hemorrhage was defined as a hematoma originating in a cerebellar hemisphere or the vermis, and brainstem hemorrhage as one originating in the midbrain, pons, or medulla oblongata. The external capsule and the putamen were grouped together, as were the globus pallidus and the internal capsule, because these structures lie in close proximity and cannot be separated reliably on computed tomography. Hematoma volume was calculated from the admission scan by the ABC/2 method [8,14]. On the axial slice with the largest area of hemorrhage, A was measured as the greatest diameter of the hematoma

and B as the largest diameter perpendicular to A, both in centimeters. C was calculated as the number of axial slices containing hemorrhage multiplied by the slice thickness in centimeters, and volume in milliliters was obtained as A × B × C / 2. Volume was measured on the admission scan, before the three-month outcome was known. When more than one scan was obtained within 48 hours of admission, the largest recorded volume was used. Intraventricular extension was recorded as present or absent.

### Outcome assessment

The primary outcome was functional outcome at three months after symptom onset, assessed with the modified Rankin Scale [19]. This scale grades global disability from 0 to 6, in which 0 indicates no symptoms, 1 no significant disability despite symptoms, 2 slight disability, 3 moderate disability with the ability to walk without assistance, 4 moderately severe disability with inability to walk or attend to bodily needs without assistance, 5 severe disability with the patient bedridden, incontinent and requiring constant nursing care, and 6 death [19]. The modified Rankin Scale was also recorded at admission. Follow-up was completed in the outpatient department or, when attendance was not possible, by a structured telephone interview. In both settings, the grade was assigned with the structured interview for the modified Rankin Scale described by Wilson and colleagues [20], which uses a fixed set of standardized questions covering constant care needs, mobility, personal care, usual activities, and symptoms. Outcome was dichotomized into good, a modified Rankin Scale score of 0-3, and poor, a score of 4-6, which is the definition of poor outcome used by Teo and colleagues and by Leasure and colleagues and therefore allows direct comparison [9,10].

### Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM Inc., Armonk, NY, USA), and validation analyses were performed in Python version 3.13. Frequency and percentage were used for categorical variables, and median with interquartile range for hematoma volume. Volume was compared with the Mann-Whitney U and Kruskal-Wallis tests, and categorical variables with the chi-squared test. Receiver operating characteristic curves were constructed for each location, and the cutoff with the highest Youden index was selected. Sensitivity and specificity with exact 95% confidence intervals were the primary accuracy measures because the quota design partly fixed prevalence. Areas under the curve were compared by the DeLong method and classification accuracy by the McNemar test. Cutoffs were internally validated with 2000 bootstrap samples and by leave-one-out cross-validation, and published thresholds were applied unchanged. Combined classification was repeated after excluding lobar hemorrhage as a sensitivity analysis. Binary logistic regression estimated odds ratios, and with 31 poor outcomes, the multivariable model was limited to the threshold and location. Calibration was assessed by the Hosmer and Lemeshow test and collinearity by variance inflation factors. No data were missing. Significance level was considered as $p < 0.05$.

### Ethics approval and consent to participate

The study was approved by the Ethical Review Committee of Dhaka Medical College Hospital, Dhaka, Bangladesh (approval no: ERC-DMC/ECC/2024/35). Written informed consent was obtained from every participant, or from a legally authorized representative when the patient was unable to give consent, after the nature, purpose, risks, and benefits of the study had been explained in the local language. The study was conducted in accordance with the Declaration of Helsinki.

## Results

Table *1* shows the profile of the 120 participants, 30 at each hemorrhage location. Ninety (75.0%) were aged 45 or above and 94 (78.3%) were men. Smoking was reported by 81 (67.5%). Hypertension was present in all, alone in 96 (80.0%) and with other conditions in 24 (20.0%). Systolic blood pressure was 140 mmHg or higher in 85 (70.8%). The Glasgow Coma Scale was 13-15 in 76 (63.3%) and intraventricular extension was present in 27 (22.5%). Median hematoma volume was 5.5 mL (interquartile range 2.3-12.4) and the median admission modified Rankin Scale was 5.

| | Frequency | Percentage |
|---|---|---|
| Age group (years) | | |
| Below 45 | 30 | 25 |
| 45 or above | 90 | 75 |
| Sex | | |
| Male | 94 | 78.3 |
| Female | 26 | 21.7 |
| Personal history | | |
| Smoking | 81 | 67.5 |

| | | |
|---|---|---|
| Alcohol consumption | 1 | 0.8 |
| Substance abuse | 12 | 10 |
| None | 26 | 21.7 |
| Comorbidity | | |
| Hypertension only | 96 | 80 |
| Multiple comorbidity | 24 | 20 |
| Systolic blood pressure (mmHg) | | |
| Below 120 | 15 | 12.5 |
| 120-139 | 20 | 16.7 |
| 140 or above | 85 | 70.8 |
| Diastolic blood pressure (mmHg) | | |
| Below 70 | 19 | 15.8 |
| 70-89 | 40 | 33.3 |
| 90 or above | 61 | 50.8 |
| Glasgow Coma Scale on admission | | |
| 13-15 | 76 | 63.3 |
| 5-12 | 43 | 35.8 |
| 3-4 | 1 | 0.8 |
| NIHSS category on admission | | |
| Minor stroke | 27 | 22.5 |
| Moderate stroke | 86 | 71.7 |
| Moderate to severe stroke | 6 | 5 |
| Severe stroke | 1 | 0.8 |
| Intracerebral hemorrhage score | | |
| 0 | 37 | 30.8 |
| 1 | 50 | 41.7 |
| 2 | 24 | 20 |
| 3 | 9 | 7.5 |
| Intraventricular extension | | |
| Present | 27 | 22.5 |
| Absent | 93 | 77.5 |
| Hematoma location | | |
| Lobar | 30 | 25 |
| Deep | 30 | 25 |
| Cerebellum | 30 | 25 |
| Brainstem | 30 | 25 |
| Hematoma volume in mL, median (IQR) | 5.5 (2.3-12.4) | |
| Modified Rankin Scale on admission, median (IQR) | 5 (4-5) | |

**TABLE 1: Baseline demographic, clinical and radiological characteristics of the study population (N = 120)**

IQR - interquartile range; NIHSS - National Institutes of Health Stroke Scale

Figure 2 shows the modified Rankin Scale at admission and at three months. At admission, 15 participants (12.5%) were in the good outcome range and 105 (87.5%) in the poor range. In total, no patient scored 0, one (0.8%) scored 1, two (1.7%) scored 2, 12 (10.0%) scored 3, 30 (25.0%) scored 4, and 75 (62.5%) scored 5, and no patient scored 6, accounting for all 120 participants. The segments for scores 1 and 2 are too narrow to carry labels in Figure 2, which is why the labeled admission values (12, 30 and 75) add up to 117. At three months, the pattern reversed, with 89 (74.2%) good and 31 (25.8%) poor outcomes. Two patients (1.7%) were free of symptoms, 18 (15.0%) had no significant disability, 30 (25.0%) had slight disability, and 39 (32.5%) had moderate disability, while 18 (15.0%) had moderately severe disability, one (0.8%) remained severely disabled, and 12 (10.0%) had died. The median score fell from 5 to 3, a significant shift ($p < 0.001$).

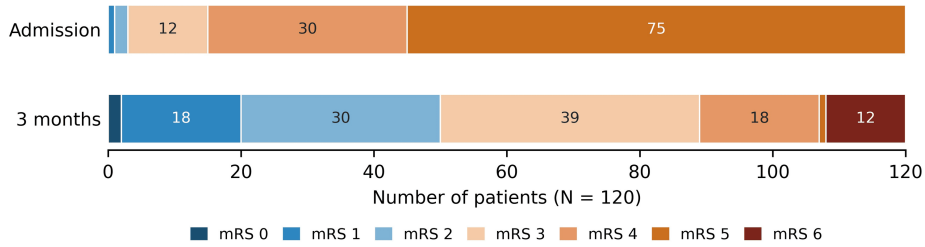



**FIGURE 2: Distribution of the modified Rankin Scale at admission and at three months in the whole cohort of 120 patients**

Numbers within the bars are patient counts

Table 2 relates admission variables to outcome. The Glasgow Coma Scale was the only clinical variable significantly associated with a poor outcome, occurring in 12 of 76 patients (15.8%) scoring 13-15, compared with 18 of 43 (41.9%) scoring 5-12 ($p = 0.002$). Stroke severity ($p = 0.253$), the intracerebral hemorrhage score ($p = 0.081$), intraventricular extension ($p = 0.312$), and hemorrhage location ($p = 0.266$) were not significant. Median hematoma volume was 5.0 mL with a good outcome and 10.0 mL with a poor outcome ($p = 0.004$).

| Variable | Good outcome (n = 89) | Poor outcome (n = 31) | p-value |
|---|---|---|---|
| Glasgow Coma Scale | | | |
| 13-15 | 64 (84.2) | 12 (15.8) | 0.002 |
| 5-12 | 25 (58.1) | 18 (41.9) | |
| 3-4 | 0 (0.0) | 1 (100.0) | |
| NIHSS category | | | |
| Minor stroke | 23 (85.2) | 4 (14.8) | 0.253 |
| Moderate stroke | 62 (72.1) | 24 (27.9) | |
| Moderate to severe stroke | 3 (50.0) | 3 (50.0) | |
| Severe stroke | 1 (100.0) | 0 (0.0) | |
| Intracerebral hemorrhage score | | | |
| 0 | 31 (83.8) | 6 (16.2) | 0.081 |
| 1 | 38 (76.0) | 12 (24.0) | |
| 2 | 16 (66.7) | 8 (33.3) | |
| 3 | 4 (44.4) | 5 (55.6) | |
| Intraventricular extension | | | |
| Present | 18 (66.7) | 9 (33.3) | 0.312 |
| Absent | 71 (76.3) | 22 (23.7) | |
| Hematoma location | | | |
| Lobar | 25 (83.3) | 5 (16.7) | 0.266 |
| Deep | 19 (63.3) | 11 (36.7) | |
| Cerebellum | 24 (80.0) | 6 (20.0) | |
| Brainstem | 21 (70.0) | 9 (30.0) | |
| Hematoma volume in mL, median (IQR) | 5.0 (2.0–10.5) | 10.0 (4.8–19.0) | 0.004 |

**TABLE 2: Admission clinical and radiological variables according to functional outcome at three months (N = 120)**

Values are presented as frequencies and percentages. A good outcome is a modified Rankin Scale score of 0-3, and a poor outcome is a score of 4-6. p-values are from the Pearson chi-squared test, except for hematoma volume, which was compared with the Mann-Whitney U test.

IQR - interquartile range; NIHSS - National Institutes of Health Stroke Scale.

Table *3* gives volume by location and outcome. Volume differed between locations (Kruskal-Wallis $p < 0.001$), the median being 12.0 mL in deep and 9.9 mL in lobar hemorrhage, compared with 4.8 mL in the cerebellum and 2.2 mL in the brainstem. After Bonferroni adjustment, brainstem volumes were the lowest, and cerebellar volumes were lower than lobar and deep volumes. Patients with a poor outcome had larger hematomas in the cerebellum (15.5 versus 3.7 mL, $p = 0.004$) and the brainstem (5.0 versus 1.9 mL, $p = 0.001$), nonsignificantly so in deep hemorrhage (15.0 versus 9.0 mL, $p = 0.089$), and the relation was reversed in lobar hemorrhage (6.0 versus 12.0 mL, $p = 0.452$). Within lobar hemorrhage, 10 of the 30 patients had a hematoma of 21 mL or more, and only one of them had a poor outcome. Of the five lobar patients with a poor outcome, three had a Glasgow Coma Scale of 5 to 12 compared with 5 of 25 with a good outcome (Fisher exact $p = 0.102$), three had an intracerebral hemorrhage score of 2 or more compared with 3 of 25 ($p = 0.041$), and one had intraventricular extension compared with 7 of 25. All five were aged 45 years or more, and two of them died with hematomas of only 1.5 and 4.0 mL.

| Location | n | Good outcome | Poor outcome | p-value |
|---|---|---|---|---|
| Lobar | 30 | 12.0 (3.8-27.5) | 6.0 (4.0-6.2) | 0.452 |
| Deep | 30 | 9.0 (5.4-14.9) | 15.0 (11.2-21.2) | 0.089 |
| Cerebellum | 30 | 3.7 (2.0-5.4) | 15.5 (7.6-23.2) | 0.004 |
| Brainstem | 30 | 1.9 (1.1-2.2) | 5.0 (3.8-6.0) | 0.001 |
| All patients | 120 | 5.0 (2.0-10.5) | 10.0 (4.8-19.0) | 0.004 |

**TABLE 3: Admission hematoma volume according to hemorrhage location and three month functional outcome**

Values are median volume in mL with interquartile range. p-values are from the Mann-Whitney U test comparing good outcomes with poor outcomes within each location. Volume differed significantly across the four locations (Kruskal-Wallis $p < 0.001$).

Figure *3* shows the receiver operating characteristic curve for each location. Discrimination was excellent for the brainstem, area under the curve 0.894 (95% CI 0.738-1.000, $p = 0.001$), and the cerebellum, 0.889 (95% CI 0.740-1.000, $p = 0.004$). It was moderate for deep hemorrhage, 0.691 (95% CI 0.480-0.903, $p = 0.085$), while the lobar curve ran below the diagonal, 0.388 (95% CI 0.053-0.723, $p = 0.436$). For the whole cohort, the area under the curve was 0.672 (95% CI 0.569-0.775, $p = 0.004$). Discrimination at each posterior fossa site was significantly better than in lobar hemorrhage ($p = 0.007$ for both comparisons), whereas the differences between the cerebellum and the brainstem ($p = 0.962$) and between deep hemorrhage and the cerebellum ($p = 0.135$) or the brainstem ($p = 0.130$) were not significant.

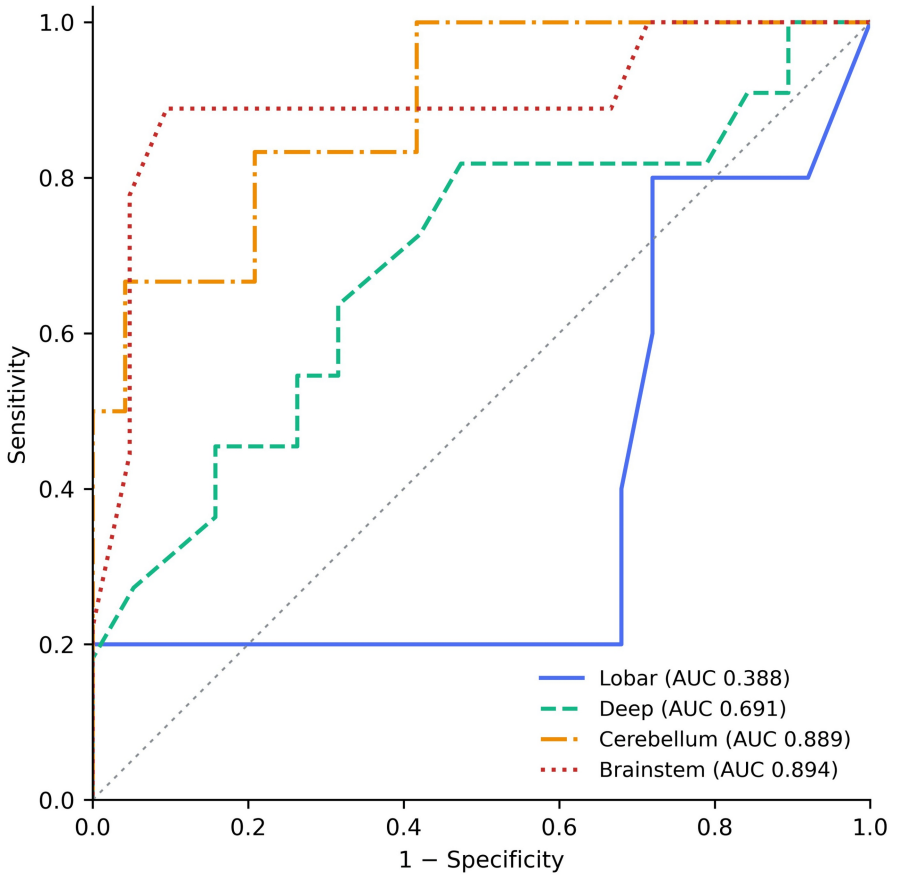



**FIGURE 3: Receiver operating characteristic curves of admission hematoma volume for predicting a poor functional outcome at three months, shown separately for lobar, deep, cerebellar and brainstem hemorrhage.**

The diagonal line represents no discrimination

Table *4* gives the cutoffs together with the area under the curve, its 95% confidence interval, and the classification performance at each cutoff. The optimal value was 2.9 mL for the brainstem (AUC 0.894, 95% CI 0.738 to 1.000), 6.1 mL for the cerebellum (AUC 0.889, 95% CI 0.740 to 1.000) and 9.8 mL for deep hemorrhage (AUC 0.691, 95% CI 0.480 to 0.903), against 3.9 mL for the whole cohort (AUC 0.672, 95% CI 0.569 to 0.775). For lobar hemorrhage, the procedure returned 39.9 mL (AUC 0.388, 95% CI 0.053 to 0.723), which is shown in Table *4* for completeness only and is not a valid threshold, because the curve lay below the diagonal and only five patients had a poor outcome. The brainstem cutoff was the most accurate (sensitivity 88.9%, 95% CI 51.8 to 99.7; specificity 90.5%, 95% CI 69.6 to 98.8; accuracy 90.0%), followed by the cerebellar cutoff (sensitivity 83.3%, 95% CI 35.9 to 99.6; specificity 79.2%, 95% CI 57.8 to 92.9; accuracy 80.0%), with a negative predictive value of 95.0% (95% CI 75.1 to 99.9) at both posterior fossa sites. The wide intervals reflect the small number of poor outcomes at each site. The deep cutoff was sensitive but not specific (81.8% and 52.6%), whereas the lobar value had a specificity of 100.0% but a sensitivity of only 20.0%. Classifying every patient against the cutoff of their own location gave a sensitivity of 74.2% (95% CI 55.4 to 88.1), specificity of 82.0% (95% CI 72.5 to 89.4) and accuracy of 80.0% (95% CI 71.7 to 86.7), compared with 83.9%, 49.4% and 58.3% for the single cutoff. The location-specific cutoffs correctly classified 32 patients who were misclassified by the single cutoff, whereas the reverse occurred in sx (McNemar $p < 0.001$), and the area under the curve of the resulting classification was 0.781 against 0.667 for the single cutoff (paired DeLong $p = 0.022$). This combined estimate includes the lobar value, which classified 29 of the 30 lobar patients as low risk and was correct in 26 of them, mainly because most lobar patients had a good outcome. In a sensitivity analysis excluding lobar hemorrhage (90 patients, 26 poor outcomes), the location specific cutoffs gave a sensitivity of 84.6% (95% CI 65.1 to 95.6), a specificity of 75.0% (95% CI 62.6 to 85.0) and an accuracy of 77.8% (95% CI 67.8 to 85.9), against 84.6%, 57.8% and 65.6% for the single cutoff of 3.9 mL in the same patients (McNemar $p = 0.013$). When lobar patients were instead classified by the single cutoff, the accuracy for all 120 patients was 67.5% against 58.3% (McNemar $p = 0.013$).

| Location | AUC (95% CI) | p-value | Cutoff (mL) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | Youden index |
|---|---|---|---|---|---|---|---|---|---|
| All patients | 0.672 (0.569-0.775) | 0.004 | 3.9 | 83.9 (66.3-94.5) | 49.4 (38.7-60.2) | 36.6 (25.5-48.9) | 89.8 (77.8-96.6) | 58.3 (49.0-67.3) | 0.333 |
| Lobar (not valid) | 0.388 (0.053-0.723) | 0.436 | 39.9 | 20.0 (0.5-71.6) | 100.0 (86.3-100.0) | 100.0 (2.5-100.0) | 86.2 (68.3-96.1) | 86.7 (69.3-96.2) | 0.200 |
| Deep | 0.691 (0.480-0.903) | 0.085 | 9.8 | 81.8 (48.2-97.7) | 52.6 (28.9-75.6) | 50.0 (26.0-74.0) | 83.3 (51.6-97.9) | 63.3 (43.9-80.1) | 0.344 |
| Cerebellum | 0.889 (0.740-1.000) | 0.004 | 6.1 | 83.3 (35.9-99.6) | 79.2 (57.8-92.9) | 50.0 (18.7-81.3) | 95.0 (75.1-99.9) | 80.0 (61.4-92.3) | 0.625 |
| Brainstem | 0.894 (0.738-1.000) | 0.001 | 2.9 | 88.9 (51.8-99.7) | 90.5 (69.6-98.8) | 80.0 (44.4-97.5) | 95.0 (75.1-99.9) | 90.0 (73.5-97.9) | 0.794 |
| Location-specific cutoffs combined | NA | NA | Own location | 74.2 (55.4-88.1) | 82.0 (72.5-89.4) | 59.0 (42.1-74.4) | 90.1 (81.5-95.6) | 80.0 (71.7-86.7) | 0.562 |
| Location-specific cutoffs, excluding lobar | NA | NA | Own location | 84.6 (65.1-95.6) | 75.0 (62.6-85.0) | 57.9 (40.8-73.7) | 92.3 (81.5-97.9) | 77.8 (67.8-85.9) | 0.596 |
| Single cutoff, excluding lobar | 0.781 (0.679-0.883) | < 0.001 | 3.9 | 84.6 (65.1-95.6) | 57.8 (44.8-70.1) | 44.9 (30.7-59.8) | 90.2 (76.9-97.3) | 65.6 (54.8-75.3) | 0.424 |

**TABLE 4: Receiver operating characteristic analysis of admission hematoma volume for predicting a poor functional outcome at three months**

Standard errors of the area under the curve were 0.053 for all patients, 0.171 for lobar, 0.108 for deep, 0.076 for cerebellar, and 0.080 for brainstem hemorrhage. A patient is classified as being at risk when the hematoma volume is at or above the cutoff. Values in parentheses below each estimate are exact 95% confidence intervals. The lobar cutoff is shown for completeness only and is not a valid threshold, because the area under the curve was below 0.5 and only five patients had a poor outcome. Predictive values depend on the proportion of patients with a poor outcome, which was partly fixed by the equal quota design. The row for location-specific cutoffs combined classifies each patient against the cutoff of their own location. The combined row for all locations includes the lobar value, which is not valid, so rows excluding lobar hemorrhage (90 patients, 26 poor outcomes) are given as a sensitivity analysis.

AUC - area under the curve; CI - confidence interval; PPV -positive predictive value; NPV - negative predictive value

Table 5 shows the unadjusted odds ratios. A hematoma at or above the cutoff of its own location carried the strongest association (odds ratio 13.12, 95% CI 4.98-34.58, $p < 0.001$), and every 5 mL increase raised the odds by 25% (1.25, 95% CI 1.03-1.54, $p = 0.028$). A Glasgow Coma Scale of 12 or below (4.05, 95% CI 1.72-9.56, $p = 0.001$) and an intracerebral hemorrhage score of 2 or above (2.49, 95% CI 1.04-5.95, $p = 0.040$) were also significant.

| Variable | Unadjusted OR (95% CI) | p value |
|---|---|---|
| Hematoma volume at or above the location specific cutoff | 13.12 (4.98-34.58) | < 0.001 |
| Hematoma volume, per 5 mL increase | 1.25 (1.03-1.54) | 0.028 |
| Hemorrhage location (lobar as reference) | | |
| Deep | 2.89 (0.86-9.74) | 0.086 |
| Cerebellum | 1.25 (0.34-4.64) | 0.739 |
| Brainstem | 2.14 (0.62-7.39) | 0.227 |
| Glasgow Coma Scale 12 or below | 4.05 (1.72-9.56) | 0.001 |
| NIHSS moderate stroke or worse | 2.35 (0.74-7.45) | 0.146 |
| Intracerebral hemorrhage score 2 or above | 2.49 (1.04-5.95) | 0.04 |
| Intraventricular extension present | 1.61 (0.64-4.10) | 0.314 |

**TABLE 5: Unadjusted binary logistic regression for a poor functional outcome at three months (N = 120)**

Each variable was entered alone in a separate binary logistic regression model with a poor outcome at three months as the dependent variable.

OR - odds ratio; CI - confidence interval; NIHSS - National Institutes of Health Stroke Scale

Table *6* shows the multivariable model. After adjustment for hemorrhage location, a hematoma at or above the cutoff of its own location remained independently associated with a poor outcome (adjusted odds ratio 19.87, 95% CI 5.66-69.81, p < 0.001). No location term was significant; the adjusted odds ratios were 0.39 (p = 0.272) for deep, 0.30 (p = 0.162) for cerebellar, and 0.67 (p = 0.610) for brainstem hemorrhage, with lobar as the reference. The model was well calibrated (Hosmer and Lemeshow chi-squared 4.02, 6 degrees of freedom, p = 0.674), and the Nagelkerke R-squared was 0.368. Variance inflation factors were 1.22 for the threshold and 1.59 to 1.84 for the location terms. Adding the three location terms to a model containing the threshold alone did not improve fit (likelihood ratio chi-squared 2.49, 3 degrees of freedom, p = 0.478), whereas adding the threshold to a model containing location alone did (chi-squared 30.60, 1 degree of freedom, p < 0.001). The association was stable in sensitivity models. With the Glasgow Coma Scale added to the threshold, the adjusted odds ratio for the threshold was 11.90 (95% CI 4.38 - 32.34) and that for a Glasgow Coma Scale of 12 or below was 3.37 (95% CI 1.25 - 9.13), and adding intraventricular extension changed neither estimate materially. When volume was entered as a continuous variable instead, each 5 mL increase carried an adjusted odds ratio of 1.47 (95% CI 1.12 - 1.94, p = 0.006), and at any given volume deep hemorrhage (adjusted odds ratio 4.52, 95% CI 1.13 - 18.15, p = 0.033) and brainstem hemorrhage (7.07, 95% CI 1.34 - 37.39, p = 0.021) carried higher odds of a poor outcome than lobar hemorrhage.

| Variable | Adjusted OR (95% CI) | p-value |
|---|---|---|
| Hematoma volume at or above the location-specific cutoff | 19.87 (5.66-69.81) | < 0.001 |
| Hemorrhage location (lobar as reference) | | |
| Deep | 0.39 (0.07-2.09) | 0.272 |
| Cerebellum | 0.30 (0.05-1.63) | 0.162 |
| Brainstem | 0.67 (0.14-3.12) | 0.61 |

**TABLE 6: Multivariable binary logistic regression for a poor functional outcome at three months**

The model contained the location-specific volume threshold and hemorrhage location only, because 31 outcome events limited the number of variables that could be entered reliably. Nagelkerke R-squared was 0.368. Hosmer and Lemeshow chi-squared was 4.02, 6 degrees of freedom, p = 0.674. Variance inflation factors were 1.22 to 1.84. Because each threshold is defined within its own location, the threshold and location terms share information, and the adjusted odds ratio should be interpreted with this in mind.

OR - odds ratio; CI - confidence interval

Table 7 shows the internal validation. After bootstrap correction, the combined location-specific classification had a sensitivity of 66.2%, a specificity of 79.6%, and an accuracy of 76.2%, with an optimism of 3.8 percentage points in accuracy, against a corrected accuracy of 56.0% for the single cutoff. The brainstem cutoff was the most stable, with a corrected accuracy of 88.0% and a bootstrap interval for the cutoff of 2.6 to 4.0 mL, whereas the cerebellar (4.1 to 17.3 mL) and deep (8.4 to 23.3 mL) cutoffs varied considerably between samples. Leave-one-out cross-validation gave a combined accuracy of 73.3%, against 55.0% for the single cutoff evaluated in the same way. Excluding lobar hemorrhage, the bootstrap-corrected accuracy was 73.7% against 61.5% for a single cutoff derived in the same 90 patients, and leave-one-out cross-validation gave 70.0% against 54.4%.

| Location | Cutoff (mL) | Bootstrap 95% interval of cutoff (mL) | Apparent Se / Sp / Acc (%) | Optimis-corrected Se / Sp / Acc (%) | Leave-one-out Se / Sp / Acc (%) |
|---|---|---|---|---|---|
| Lobar | 39.9 | NA | 20.0 / 100.0 / 86.7 | 7.1 / 97.5 / 83.8 | 20.0 / 96.0 / 83.3 |
| Deep | 9.8 | 8.4-23.3 | 81.8 / 52.6 / 63.3 | 73.5 / 47.5 / 57.1 | 45.5 / 52.6 / 50.0 |
| Cerebellum | 6.1 | 4.1-17.3 | 83.3 / 79.2 / 80.0 | 71.4 / 76.8 / 75.9 | 50.0 / 79.2 / 73.3 |
| Brainstem | 2.9 | 2.6-4.0 | 88.9 / 90.5 / 90.0 | 84.3 / 89.6 / 88.0 | 77.8 / 90.5 / 86.7 |
| Location-specific cutoffs combined | Own location | NA | 74.2 / 82.0 / 80.0 | 66.2 / 79.6 / 76.2 | 51.6 / 80.9 / 73.3 |
| Single cutoff, all patients | 3.9 | 2.4-12.8 | 83.9 / 49.4 / 58.3 | 79.5 / 47.9 / 56.0 | 80.6 / 46.1 / 55.0 |
| Location-specific cutoffs, excluding lobar | Own location | NA | 84.6 / 75.0 / 77.8 | 76.6 / 72.4 / 73.7 | 57.7 / 75.0 / 70.0 |
| Single cutoff, excluding lobar | 3.7 | 2.4-12.8 | 88.5 / 54.7 / 64.4 | 83.1 / 52.6 / 61.5 | 57.7 / 53.1 / 54.4 |

**TABLE 7: Internal validation of the location specific cutoffs by bootstrap resampling and leave one out cross validation**

Two thousand bootstrap samples were drawn with replacement within each location, keeping 30 patients per location, and the cutoff was derived again in each sample. Optimism is the mean difference between the performance of the rederived cutoff in the bootstrap sample and in the original cohort, and it was subtracted from the apparent performance. In leave-one-out cross-validation, each patient was classified by a cutoff derived without that patient. The bootstrap interval for the lobar cutoff is not reported because the lobar curve lay below the diagonal. Rows excluding lobar hemorrhage are a sensitivity analysis in 90 patients, with the single cutoff derived again in these patients.

Se - sensitivity; Sp - specificity; Acc - accuracy; NA - not applicable

Table 8 shows the published thresholds applied to our cohort. The brainstem threshold of 2.0 mL reported by

Ironside and colleagues had the same sensitivity as our 2.9 mL cutoff (88.9%) but a lower specificity (52.4% against 90.5%). Their cerebellar threshold of 12.0 mL was fully specific but detected only three of six poor outcomes, and their lobar and deep thresholds performed poorly. Applied across all four locations, their thresholds gave a sensitivity of 67.7%, a specificity of 65.2%, and an accuracy of 65.8%, and after excluding lobar hemorrhage, an accuracy of 68.9% against 77.8% for our thresholds. The poor outcome thresholds of Teo and colleagues were fully specific but detected only four of 20 poor outcomes in the three locations to which they could be applied. For deep hemorrhage, the 8 mL threshold of Leasure and colleagues was sensitive but not specific (81.8% and 42.1%), and their 18 mL threshold was specific but insensitive (84.2% and 45.5%).

| Threshold source | Location | Threshold (mL) | Sensitivity, % (n/N) | Specificity, % (n/N) | Accuracy, % (n/N) |
|---|---|---|---|---|---|
| Present study | Lobar | 39.9 | 20.0 (1/5) | 100.0 (25/25) | 86.7 (26/30) |
| | Deep | 9.8 | 81.8 (9/11) | 52.6 (10/19) | 63.3 (19/30) |
| | Cerebellum | 6.1 | 83.3 (5/6) | 79.2 (19/24) | 80.0 (24/30) |
| | Brainstem | 2.9 | 88.9 (8/9) | 90.5 (19/21) | 90.0 (27/30) |
| | All four locations | Own location | 74.2 (23/31) | 82.0 (73/89) | 80.0 (96/120) |
| | Excluding lobar | Own location | 84.6 (22/26) | 75.0 (48/64) | 77.8 (70/90) |
| Ironside et al. [11] | Lobar | 21.0 | 20.0 (1/5) | 64.0 (16/25) | 56.7 (17/30) |
| | Deep | 7.0 | 81.8 (9/11) | 36.8 (7/19) | 53.3 (16/30) |
| | Cerebellum | 12.0 | 50.0 (3/6) | 100.0 (24/24) | 90.0 (27/30) |
| | Brainstem | 2.0 | 88.9 (8/9) | 52.4 (11/21) | 63.3 (19/30) |
| | All four locations | Own location | 67.7 (21/31) | 65.2 (58/89) | 65.8 (79/120) |
| | Excluding lobar | Own location | 76.9 (20/26) | 65.6 (42/64) | 68.9 (62/90) |
| Teo et al. [9] | Lobar | 48 | 0.0 (0/5) | 100.0 (25/25) | 83.3 (25/30) |
| | Cerebellum | 22 | 33.3 (2/6) | 100.0 (24/24) | 86.7 (26/30) |
| | Brainstem | 7.5 | 22.2 (2/9) | 100.0 (21/21) | 76.7 (23/30) |
| | Three locations | Own location | 20.0 (4/20) | 100.0 (70/70) | 82.2 (74/90) |
| Leasure et al. [10] | Deep (thalamic value) | 8 | 81.8 (9/11) | 42.1 (8/19) | 56.7 (17/30) |
| | Deep (basal ganglia value) | 18 | 45.5 (5/11) | 84.2 (16/19) | 70.0 (21/30) |

**TABLE 8: Performance of previously published location specific thresholds when applied to the present cohort**

A patient is classified as being at risk when the hematoma volume is at or above the threshold. The published thresholds were applied without modification. Ironside and colleagues defined a poor outcome as a modified Rankin Scale score above 2 at 90 days, Teo and colleagues as a score of 4-6 at six months, and Leasure and colleagues as a score of 4-6, whereas the present study used a score of 4-6 at three months. The deep thresholds of Teo and colleagues are specific to subregions of the basal ganglia and thalamus and could not be applied, and the thalamic and basal ganglia values of Leasure and colleagues were each applied to all deep hemorrhages. The present lobar value is not a valid threshold and is shown for comparison only.

## Discussion

The present study indicated that, in conservatively managed patients, the hematoma volume predicting a poor three-month outcome after acute primary intracerebral hemorrhage varied markedly with hemorrhage location. Even small hematomas in the brainstem and cerebellum were associated with a poor outcome, whereas lobar hemorrhage showed no relationship between volume and outcome. Location-specific cutoffs classified patients more accurately than a single global threshold, and this advantage persisted after internal validation and after excluding the invalid lobar cutoff.

The posterior fossa findings are the most striking and readily explained. That compartment is small, bounded by rigid bone and the tentorium, and holds the fourth ventricle and the brainstem within a few centimeters of each other, so a few milliliters of blood cause tract interruption, fourth ventricular obstruction, and compression of structures that sustain consciousness and respiration [21]. Our brainstem

threshold of 2.9 mL is close to the 2.0 mL reported by Ironside et al. but lower than the 7.5 mL reported by Teo et al. for a poor six-month outcome [9,11]. Our cerebellar threshold of 6.1 mL is lower than the 12.0 mL and 22 mL in those cohorts [9,11], and when their values were applied to our patients, they were fully specific but missed half or more of the poor outcomes. The likely reason is that we excluded operated patients. Where evacuation is available, hematomas above roughly 12 to 15 mL are usually operated on and their outcomes partly rescued, which shifts the observed threshold upward [22,23].

For deep hemorrhage, the threshold of 9.8 mL falls between the 8 mL for thalamic and 18 mL for basal ganglia hemorrhage reported by Leasure and colleagues, as expected when these subsites are pooled [10]. Discrimination was only moderate, and the bootstrap interval of the cutoff was wide, so this value remains provisional. Lobar hemorrhage yielded no usable threshold, and only 5 of 30 such patients had a poor outcome. Ten lobar patients had hematomas of 21 mL or more, yet only one of them had a poor outcome, so a truncated range of volumes does not fully explain this finding. The poor lobar outcomes appeared to be driven by factors other than volume, since three of the five patients had a reduced level of consciousness and an intracerebral hemorrhage score of 2 or more, and two died with hematomas of only 1.5 and 4.0 mL. Outcome after lobar hemorrhage also depends on which lobe and gyrus are involved, information that raw volume does not capture [24]. With so few events, the inverse relation is most likely a chance finding.

Hematoma volume remained associated with poor outcome after adjustment for location, both as a continuous variable and as a location-specific threshold. Because each threshold is defined within its own location, it already carries much of the prognostic information of location. When volume was continuous, deep and brainstem hemorrhage carried higher odds of a poor outcome at any given volume, whereas the location terms added nothing once volume was scaled to its location threshold. The adjusted odds ratio of 19.87 therefore does not show that the threshold acts independently of location. It shows that scaling volume to the tolerance of each compartment captures the effect of location, which supports the view that location matters mainly by changing how much blood a patient can tolerate [9].

The practical value of these thresholds lies in settings like ours, where the admission computed tomography scan is often the only investigation. A brainstem hematoma above 2.9 mL or a cerebellar hematoma above 6.1 mL marks a patient who needs a high dependency bed, close neurological monitoring, an early neurosurgical opinion and a frank conversation with the family. The cerebellar threshold lies well below the 15 mL at which current guidelines recommend surgical evacuation [14], so patients between these values are at substantial risk before they meet surgical criteria. These thresholds should inform intensity of care and trial design, since protocolized medical care improves outcome across the whole population [25] whereas surgical benefit has been shown only for selected locations [26]. They are best used alongside the Glasgow Coma Scale and the intracerebral hemorrhage score [7], and they should not alone justify withdrawal of treatment, because prognostic pessimism applied early can become self-fulfilling [6]. Before the thresholds are built into a clinical decision rule or a location-based score, they need external validation in unselected multicenter cohorts, comparison with the intracerebral hemorrhage score, and an impact study.

This study has several strengths. To the best of our knowledge, it is the first prospective study from Bangladesh to report hematoma volume cutoffs separately for lobar, deep, cerebellar, and brainstem hemorrhage, and outcomes were recorded prospectively at a fixed time point. However, our study had some limitations. First, it was a single-center study with purposive quota sampling, so the case mix and the predictive values may not reflect unselected admissions, and the number of patients screened and excluded was not captured. Second, operated patients were excluded, so the thresholds apply only to conservatively managed patients. Third, the cutoffs were derived and tested in the same cohort, and the cerebellar and deep cutoffs were unstable on bootstrap validation. Fourth, the sample size calculation used the prevalence of deep hemorrhage instead of a poor outcome, so the study was underpowered, and with only 5-11 poor outcomes per location, the thresholds are imprecise, and the multivariable model was limited. Fifth, follow-up ended at three months, so outcomes at six and twelve months were not assessed. Sixth, premorbid disability, including musculoskeletal conditions, was not recorded and may have contributed to disability at three months. Finally, the ABC/2 method overestimates irregular hematomas; interobserver agreement was not assessed, and the specific lobe involved in lobar hemorrhage was not recorded.

## Conclusions

In conservatively managed patients with acute primary intracerebral hemorrhage, the hematoma volume separating a good from a poor three-month outcome differed markedly by location, with cutoffs of 2.9 mL for the brainstem, 6.1 mL for the cerebellum, and a provisional 9.8 mL for deep hemorrhage. No reliable cutoff could be derived for lobar hemorrhage. Location-specific cutoffs classified patients more accurately than a single global cutoff, and this advantage persisted after internal validation and after excluding lobar hemorrhage. Because the thresholds came from a small single-center sample with few poor outcomes and excluded operated patients, they should not guide clinical decisions until they are confirmed. Larger multicenter studies with external validation are needed in South Asian populations.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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## Disclosures

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