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Intracerebral hemorrhage location and outcome among INTERACT2 participants

ABSTRACT

Objective: To clarify associations between intracerebral hemorrhage (ICH) location and clinical outcomes among participants of the main phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods: Associations between ICH sites and poor outcomes (death \([8]\) or major disability \([3–5]\) of modified Rankin Scale) and European Quality of Life Scale (EQ-5D) utility scores at 90 days were assessed in logistic regression models.

Results: Of 2,066 patients included in the analyses, associations were identified between ICH sites and poor outcomes: involvement of posterior limb of internal capsule increased risks of death or major disability (odds ratio [OR] 2.10) and disability (OR 1.81); thalamic involvement increased risks of death or major disability (OR 2.24) and death (OR 1.97). Involvement of the posterior limb of the internal capsule, thalamus, and infratentorial sites were each associated with poor EQ-5D utility score (\(<=0.7\) median; OR 1.87, 2.14, and 2.81, respectively). Posterior limb of internal capsule involvement was strongly associated with low scores across all health-related quality of life domains. ICH encompassing the thalamus and posterior limb of internal capsule were associated with death or major disability, major disability, and poor EQ-5D utility score (OR 1.72, 2.26, and 1.71, respectively).

Conclusion: Poor clinical outcomes are related to ICH affecting the posterior limb of internal capsule, thalamus, and infratentorial sites. The highest association with death or major disability and poor EQ-5D utility score was seen in ICH encompassing the thalamus and posterior limb of internal capsule.


GLOSSARY

\(BP\) = blood pressure; \(CI\) = confidence interval; \(EQ-5D\) = European Quality of Life Scale; \(HRQoL\) = health-related quality of life; \(ICH\) = intracerebral hemorrhage; \(IQR\) = interquartile range; \(IVH\) = intraventricular hemorrhage; \(INTERACT2\) = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; \(mRS\) = modified Rankin Scale; \(NIHSS\) = NIH Stroke Scale; \(OR\) = odds ratio.

The prognosis for recovery from acute intracerebral hemorrhage (ICH) is strongly related to several radiologic criteria. These include hematoma volume and the degree of extension of blood into the ventricles and the subarachnoid space.1–3 Infratentorial location of ICH also predicts a higher likelihood of death or dependency.1,4 However, the relationship between specific

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locations of supratentorial ICH and outcome is poorly understood due in part to varying
designs and definitions across studies. We examined associations of ICH location with
clinical outcomes among participants of the main phase Intensive Blood Pressure Reduc-
tion in Acute Cerebral Hemorrhage Trial (INTERACT2).

METHODS Patients. The INTERACT2 study was a random-
ized, open, multicenter, controlled trial with blinded outcome
assessment conducted between 2008 and 2012. A total of
2,839 patients with imaging-confirmed ICH were randomly
assigned to receive either early intensive blood pressure (BP)-
lowering treatment (<140 mm Hg systolic BP goal) or the
contemporaneous guideline-recommended BP management
(<180 mm Hg systolic BP goal) within 6 hours of onset.
Follow-up was to 90 days.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the appropriate
ethics committee at each participating site, and written informed con-
sent was obtained from patients or appropriate surrogates. INTER-
ACT2 is registered with ClinicalTrials.gov (NCT00716079).

Measures. Demographic and clinical characteristics were re-
corded upon patient enrollment. CT scans were performed ac-
cording to standardized techniques (recommended slice
thickness: 5–8 mm) at baseline and centrally analyzed for volume
and location of ICH and the presence of intraventricular hemor-
rhage (IVH) extension.

Three neurologists reviewed all CT scans for detailed assess-
ment of sites involved by each ICH. Defined sites were the cau-
date head, putamen/globus pallidus, thalamus, posterior limb of
internal capsule, anterior limb of internal capsule, external cap-
sule, any lobar region, and infratentorial. ICH could involve
one or several sites. For small bleeds confined to any site, that site
was classified as involved. For 3 well-delimited sites (caudate
head, putamen/globus pallidus, and thalamus), involvement
was defined as replacement of over one-third of the structure
by blood (judgment made by assessor on CT scan axial slices).
For the remaining sites, posterior limb of internal capsule, ante-
rior limb of internal capsule, external capsule, any lobar location,
and infratentorial any involvement led to these sites being classi-
fied as affected. Superficial supratentorial or lobar location was
selected when structures other than deep structures (caudate
head, putamen/globus pallidus, thalamus, internal capsule) were
affected. In large volume ICH, where the hemorrhage spanned the hemi-
sphere from the ventricle to the cortex, location was rated as both
deep, with affected sites listed, and lobar. ICH were then evalu-
ated for their entire location, which could involve single or mul-
tiple sites. The term encompassing has been used to describe
common patterns of ICH that involve one or more of the sites
defined above.

Outcomes for these analyses were death or major disability as
assessed by the modified Rankin Scale (mRS) (death, score of 6;
major disability, score of 3–5) and health-related quality of life
(HRQoL) as self-assessed by the patient or by a proxy responder
using the EuroQol Group’s EuroQol-5D questionnaire at 90 days.
The EQ-5D uses a descriptive system defining the state of general health across 5 dimensions (mobility, self-care,
usual activities, pain/discomfort, and anxiety/depression), with
respondents rating their assessment of each as having no (score
of 1), some or moderate (score of 2), or severe problems (score of
3). A utility score integrating ratings of the 5 dimensions into
a single score was calculated by using population-based preference
weights obtained from the UK population for each subscale. The
utility score expresses HRQoL quantitatively as a fraction of
perfect health: a score of 1 represents perfect health, 0 represents
death, and negative scores represent health states considered
worse than death; a score between 0.8 and 0.9 represents the
average score in the general population. Both measures were
used in the present analysis.

Statistical analysis. Baseline characteristics of included and
excluded patients were summarized by means and SD for normally
distributed variables, medians and interquartile ranges (IQR) for
skewed continuous variables, and numbers (%) for categorical
variables. Between-group differences were assessed using the χ² test
for categorical variables and the Wilcoxon test for continuous variables.
Associations between ICH sites of involvement and death or major
disability, poor HRQoL in each domain, grades of some to
moderate or severe vs no problems in the corresponding
dimensions, and poor overall HRQoL (utility score ≤0.7
[dichotomized by median]) were assessed in multivariable logistic
regression models, adjusted for potential confounders. The adjusted
variables included age, female sex, China region of recruitment,
history of ischemic stroke and diabetes mellitus, medication
history of antihypertensives, antithrombotics, and lipid-lowering
agents, NIH Stroke Scale (NIHSS) score (log-transformed), baseline hematoma volume (log-transformed), IVH,
location to intensive BP lowering, laterality (left vs right),
and proxy response for the HRQoL models. Each individual site
caudate head, putamen/globus pallidus, thalamus, external
capsule, anterior limb of internal capsule, posterior limb of
internal capsule, lobar, and infratentorial) was included in the
multivariable model to identify independent relationships
between specific sites and outcome. The same analysis was
repeated without adjusting for NIHSS. Also, common patterns
of entire ICH encompassing one or multiple sites were included
in a multivariable model adjusted for the same variables except
individual sites. A standard level of significance (p < 0.05) was
used and the data are reported with odds ratios (OR) and 95%
confidence intervals (CI). All analyses were performed using SAS
software version 9.3 (SAS Institute, Cary, NC).

RESULTS Among the 2,829 INTERACT2 partici-
pants, 2,066 (73%) were included in the mortality and
functional outcome analyses with available baseline
dICOM format CT and information on outcome
(mRS) at 90 days (figure e-1 at Neurology.org).
Table 1 shows the baseline characteristics of included and
excluded patients; the former had smaller ICH
(median 10.7 [IQR 5.6–18.7] mL vs 12.0 [6.3–23.9] mL)
and were more likely to answer the EQ-5D questions
themselves (fewer proxy responders, indicative of
less severe ICH).

Table e-1 shows the most common patterns of
ICH. Entire ICH included 56 combinations of possi-
ble sites. Of these possible combinations, 42 (75%)
were present in fewer than 10 patients, 6 (11%) in
between 10 and 50 patients, and 8 (14%) in more than
130 patients (total n = 1,747, 85% of the total pop-
ulation). The most common patterns were putamen/
Abbreviations: BP = blood pressure; HRQoL = health-related quality of life; IQR = interquartile range; NIHSS = NIH Stroke Scale.

Data are n (%) unless stated otherwise.

*p Value χ² test for categorical variables and Wilcoxon test for continuous variables.

Table 1 Characteristics of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) participants included in and excluded from the analyses

<table>
<thead>
<tr>
<th>Included (n = 2,066)</th>
<th>Excluded (n = 763)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>64 ± 13</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Female</td>
<td>772 (37)</td>
<td>277 (36)</td>
</tr>
<tr>
<td>China region</td>
<td>1,381 (67)</td>
<td>539 (71)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>160 (8)</td>
<td>69 (9)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>211 (10)</td>
<td>75 (10)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,489 (72)</td>
<td>559 (73)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>230 (11)</td>
<td>75 (10)</td>
</tr>
<tr>
<td><strong>Medication history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>953 (46)</td>
<td>321 (42)</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>254 (12)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>151 (7)</td>
<td>51 (7)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from onset to CT, h, median (IQR)</td>
<td>1.8 (1.2–2.7)</td>
<td>1.8 (1.2–2.7)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg, mean ± SD</td>
<td>179 ± 17</td>
<td>179 ± 17</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg, mean ± SD</td>
<td>101 ± 15</td>
<td>102 ± 15</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>11 (6–16)</td>
<td>10 (6–15)</td>
</tr>
<tr>
<td><strong>CT findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma volume, mL, median (IQR)</td>
<td>10.7 (6.6–18.7)</td>
<td>12.0 (6.3–23.9)</td>
</tr>
<tr>
<td>Left hemisphere ICH</td>
<td>1,059 (51)</td>
<td>254 (48)</td>
</tr>
<tr>
<td><strong>Involved locations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate head</td>
<td>42 (2)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>640 (31)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Putamen/globus pallidus</td>
<td>1,161 (56)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>External capsule</td>
<td>553 (27)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>102 (5)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>957 (46)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Lobar</td>
<td>297 (14)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>141 (7)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>595 (29)</td>
<td>145 (27)</td>
</tr>
<tr>
<td>Randomized intensive BP lowering</td>
<td>1,031 (50)</td>
<td>368 (48)</td>
</tr>
<tr>
<td>Proxy responder at 90-day HRQoL assessment</td>
<td>728 (40)</td>
<td>227 (48)</td>
</tr>
</tbody>
</table>

For analysis of HRQoL, 251 patients who died within 90 days and 36 without EQ-5D information were excluded, leaving 1,779 patients for analysis of HRQoL (figure e-1). Table 3 shows associations between ICH location and HRQoL. After adjusting for potential confounders, thalamic OR 2.14 (95% CI 1.32–3.48), posterior limb of internal capsule OR 1.87 (95% CI 1.45–2.40), and infratentorial OR 2.81 (95% CI 1.52–5.20) sites were each associated with poor overall HRQoL (utility score ≤0.7). Posterior limb of internal capsule was associated with poor HRQoL across all domains. Thalamic and infratentorial sites were associated with poor HRQoL in the mobility, self-care, and usual activity domains.

Table 4 shows associations between the most common patterns of entire ICH and death or disability at 90 days. After adjustment for potential confounders, ICH encompassing the thalamus and posterior limb of internal capsule were associated with death or major disability (OR 1.72 [95% CI 1.14–2.58]) and major disability (2.26 [1.58–3.23]). ICH encompassing the posterior limb of internal capsule and putamen/globus pallidus with or without additional involvement of the external capsule were associated with disability (OR 1.69 [95% CI 1.13–2.54] and 1.52 [1.04–2.21]).

Table 5 shows associations between the most common patterns of entire ICH and HRQoL. After adjustment for potential confounders, ICH encompassing the thalamus and posterior limb of internal capsule were associated with poor EQ-5D utility score (≤0.7 [median]; OR 1.71 [95% CI 1.12–2.60]) and putamen/globus pallidus and external capsule (n = 153), and infratentorial alone (n = 138).
antithrombotics, and lipid-lowering agents, NIH Stroke Scale score (0.78, 0.83, 0.82, 0.66, and 0.69, respectively.

and proxy responders. The lobar, infratentorial, and intraventricular extension of hematoma, ICH laterality, randomization to intensive blood pressure hematoma volume (log-transformed), caudate head, thalamus, putamen/globus pallidus, external capsule, anterior and posterior limbs of internal capsule, the usual activity and pain/discomfort domains: OR 2.08 (95% CI 1.34–3.22), 2.26 (1.42–3.60), and 1.78 (1.21–2.62), respectively. Thalamic ICH was associated with poor HRQoL in the mobility and usual activity domain: poor HRQoL in the self-care, usual activity, and pain/discomfort domains: OR 2.08 (95% CI 1.34–3.22), 2.26 (1.42–3.60), and 1.78 (1.21–2.62), respectively.

Table 3

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate head</td>
<td>42</td>
<td>0.26</td>
<td>0.08-0.82^a</td>
<td>1.59</td>
<td>0.57-4.47</td>
<td>0.28</td>
<td>0.09-0.89^a</td>
<td>0.32</td>
</tr>
<tr>
<td>Thalamus</td>
<td>640</td>
<td>2.14</td>
<td>1.32-3.48^b</td>
<td>2.42</td>
<td>1.45-4.05^c</td>
<td>2.28</td>
<td>1.37-3.82^b</td>
<td>3.00</td>
</tr>
<tr>
<td>Putamen/globus pallidus</td>
<td>1,161</td>
<td>1.27</td>
<td>0.80-2.02</td>
<td>1.34</td>
<td>0.81-2.20</td>
<td>1.24</td>
<td>0.76-2.02</td>
<td>1.59</td>
</tr>
<tr>
<td>External capsule</td>
<td>553</td>
<td>0.98</td>
<td>0.73-1.33</td>
<td>1.16</td>
<td>0.86-1.57</td>
<td>1.19</td>
<td>0.87-1.62</td>
<td>1.17</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>102</td>
<td>1.33</td>
<td>0.70-2.53</td>
<td>0.72</td>
<td>0.38-1.35</td>
<td>1.12</td>
<td>0.58-2.18</td>
<td>0.79</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>957</td>
<td>1.87</td>
<td>1.45-2.40^d</td>
<td>1.54</td>
<td>1.19-1.99^e</td>
<td>2.04</td>
<td>1.57-2.65^d</td>
<td>1.70</td>
</tr>
<tr>
<td>Lobar</td>
<td>297</td>
<td>1.18</td>
<td>0.74-1.87</td>
<td>1.23</td>
<td>0.74-2.03</td>
<td>1.08</td>
<td>0.66-1.76</td>
<td>1.51</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>141</td>
<td>2.81</td>
<td>1.52-5.20^b</td>
<td>4.03</td>
<td>2.16-7.50^c</td>
<td>2.57</td>
<td>1.35-4.87^b</td>
<td>3.66</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; No. = number of cases by ICH location; OR = odds ratio.

Multivariable models were adjusted for age, female sex, China region, history of ischemic stroke and diabetes, medication history of antihypertensives, antithrombotics, and lipid-lowering agents, NIH Stroke Scale score (≤11 vs <11), systolic blood pressure, onset to CT time (log-transformed), baseline hematoma volume (log-transformed), caudate head, thalamus, putamen/globus pallidus, external capsule, anterior and posterior limbs of internal capsule, lobar, infratentorial, and intraventricular extension of hematoma, ICH laterality, and randomization to intensive blood pressure-lowering management policy, and proxy responders. The c statistics for the models of utility score, mobility, self-care, usual activity, pain/discomfort, and anxiety/depression were 0.79, 0.78, 0.83, 0.82, 0.66, and 0.69, respectively.

Table 2

<table>
<thead>
<tr>
<th>ICH sites of involvement</th>
<th>Death or major disability</th>
<th>Major disability</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Caudate head</td>
<td>42</td>
<td>0.42</td>
<td>0.16-1.14</td>
</tr>
<tr>
<td>Thalamus</td>
<td>640</td>
<td>2.24</td>
<td>1.40-3.57^b</td>
</tr>
<tr>
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<td>553</td>
<td>1.05</td>
<td>0.78-1.40</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>102</td>
<td>1.03</td>
<td>0.56-1.91</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>957</td>
<td>2.10</td>
<td>1.65-2.68^b</td>
</tr>
<tr>
<td>Lobar</td>
<td>297</td>
<td>1.34</td>
<td>0.86-2.08</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>141</td>
<td>3.04</td>
<td>1.68-5.50^b</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; No. = number of cases by ICH location; OR = odds ratio.

Multivariable models were adjusted for age, female sex, China region, history of ischemic stroke and diabetes, medication history of antihypertensives, antithrombotics, and lipid-lowering agents, NIH Stroke Scale score (≤11 vs <11), systolic blood pressure, onset to CT time (log-transformed), baseline hematoma volume (log-transformed), caudate head, thalamus, putamen/globus pallidus, external capsule, anterior and posterior limbs of internal capsule, lobar, infratentorial, and intraventricular extension of hematoma, ICH laterality, and randomization to intensive blood pressure-lowering management policy, and proxy responders. The c statistics for the models of death or major disability, major disability, and death were 0.83, 0.72, and 0.82, respectively.

*p < 0.01.

*0.01 ≤ p ≤ 0.05.

**p < 0.001.
The lowering agents, NIH Stroke Scale score (Multivariable models were adjusted for age, female sex, China region, history of ischemic ability, and death were 0.82, 0.72, and 0.82, respectively.

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; OR = odds ratio. Multivariable models were adjusted for age, female sex, China region, history of ischemic stroke and diabetes, medication history of antihypertensives, antithrombotics, and lipid-lowering agents, NIH Stroke Scale score (≥11 vs ≤11), systolic blood pressure, onset to CT time (log-transformed), baseline hematoma volume (log-transformed), intraventricular extension of ICH, ICH laterality, and randomization to intensive blood pressure-lowering management policy. The c statistics for the models of death or major disability, major disability, and death were 0.82, 0.72, and 0.82, respectively.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Death or major disability</th>
<th>Major disability</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Thalamus</td>
<td>181 1.02 0.64–1.63</td>
<td>1.32 0.86–2.01</td>
<td>1.21 0.65–2.24*</td>
</tr>
<tr>
<td>Putamen</td>
<td>342 0.44 0.29–0.65b</td>
<td>0.69 0.48–0.99*</td>
<td>0.50 0.28–0.90</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>138 1.31 0.77–2.22</td>
<td>1.32 0.81–2.16</td>
<td>1.23 0.55–2.74</td>
</tr>
<tr>
<td>Lobar</td>
<td>181 0.44 0.27–0.71b</td>
<td>0.60 0.39–0.92*</td>
<td>0.67 0.39–1.17</td>
</tr>
<tr>
<td>Thalamus and posterior limb of internal capsule</td>
<td>339 1.72 1.14–2.58c</td>
<td>2.26 1.58–3.23c</td>
<td>0.71 0.42–1.22</td>
</tr>
<tr>
<td>Putamen/globus pallidus and posterior limb of internal capsule</td>
<td>177 1.32 0.83–2.11</td>
<td>1.69 1.13–2.54c</td>
<td>0.66 0.35–1.24</td>
</tr>
<tr>
<td>Putamen/globus pallidus and external capsule</td>
<td>153 0.56 0.35–0.91</td>
<td>0.95 0.61–1.46</td>
<td>0.45 0.21–0.96*</td>
</tr>
<tr>
<td>Putamen/globus pallidus, posterior limb of internal capsule and external capsule</td>
<td>236 1.07 0.69–1.65</td>
<td>1.52 1.04–2.21*</td>
<td>0.57 0.33–1.01</td>
</tr>
</tbody>
</table>

OR 1.78 (95% CI 1.02–3.10) and 1.86 (1.06–3.26). ICH encompassing the putamen/globus pallidus, posterior limb of internal capsule, and external capsule were associated with poor HRQoL in the pain/discomfort domain: OR 1.65 (95% CI 1.10–2.47).

Table e-6 shows the hematoma volume by site of involvement and table e-7 shows the model fit statistics for tables 2 and 3.

DISCUSSION

This secondary analysis of the INTERACT2 study dataset demonstrates strong associations between the location of ICH and clinically relevant, patient-centered outcomes. Any ICH that involves the posterior limb of internal capsule or thalamus increases the risks of death or disability and of disability alone. ICH involving the posterior limb of the internal capsule, thalamus, and infratentorial sites were each associated with poor HRQoL. In particular, involvement of the posterior limb of the internal capsule was strongly associated with poor outcomes across all HRQoL domains. Of the 8 common recognizable patterns of ICH, the striking characteristic is that all of these that involve the posterior limb of internal capsule are associated with major disability. Isolated thalamic hemorrhage and ICH encompassing the thalamus and posterior limb of internal capsule are associated with poor HRQoL. These data indicate that damage to the capsular pyramidal tracts is particularly disabling, while ICH involving the thalamus and posterior fossa are more likely to be fatal. In contrast, ICH confined to a lobar site seems to have a relatively benign prognosis when adjusted for hemorrhage volume. However, this does not necessarily mean that outcome after a capsular ICH is worse than outcome after a lobar ICH, as mean hemorrhage volume in lobar ICH is large by comparison with deep ICH and volume itself is an important predictor of outcome. When looking at ICH that involved a lobar site and one or more other sites, there is an increased risk of death. This is likely to reflect the fact that these are extensive ICH spanning from deep structures to the cortex. Finally, the analysis confirms well-recognized associations between older age, higher neurologic severity, ICH volume, and poor outcomes.

There is increasing interest in the assessment of HRQoL after stroke, but there has been limited data on its association with ICH in specific brain locations. In the Factor VII for Acute Intracerebral Hemorrhage trial, deep compared to lobar location of ICH was associated with poor HRQoL, but no further assessment of anatomical structures was undertaken.

Damage to the posterior limb of the internal capsule on diffusion tensor tractography has been shown to be related to poor motor outcome and to disability in the ischemic stroke literature, while ICH in the thalamus has been shown to be associated with higher in-hospital mortality compared to ICH in other supratentorial locations. The pyramidal tracts pass through the posterior limb of the internal capsule location and pathology affecting motor function has predictable consequences for disability and HRQoL related directly to domains of mobility, usual activity, and self-care, and indirectly to the more subjective domains of pain/discomfort and anxiety/depression. Thalamic ICH is prone to leak blood into the ventricles and may extend to compress the brainstem with life-threatening consequences. Greater residual neurologic deficit may explain why survivors of ICH involving the posterior limb of internal capsule, thalamus, and infratentorium had worse overall HRQoL compared to those who recover from ICH in other locations. The finding that the domains of pain/discomfort and anxiety/depression showed no significant associations with thalamic involvement and a very weak association for the former with thalamic ICH in the multivariable models is surprising. Strokes in the thalamus have a high
incidence of residual sensory disability and are traditionally associated with pain syndromes,\textsuperscript{19} while lesions of spinothalamic afferents to the posterior thalamus are associated with development of central pain.\textsuperscript{20} This effect seems small in ICH.

Strengths of our analysis include the assessment of HRQoL in a large group of participants with ICH with rigorous and structured central adjudication of images for determining ICH location. Limitations include selection bias from a clinical trial population where patients with severe ICH were purposefully excluded. From a practical point of view, the excluded patients were those with a very high likelihood of early death, so they might be expected to influence mortality calculations but not necessarily HRQoL outcomes. Another issue is that ICH location was assessed on varying thicknesses of axial slices of brain CT scans, which adds some noise to the data but probably not of sufficient magnitude to bias the observed changes in one particular site over another. There was a small number of infratentorial and lobar ICH, not allowing for further anatomical segmentation of these compartments. Despite the large size of the INTERACT dataset, when individual complete hemorrhage is analyzed the numbers are reduced to the point where less powerful effects no longer reach significance. Again, this affects mortality analysis more than disability for the reasons stated above.

We have shown that specific ICH sites, namely the posterior limb of the internal capsule, thalamus, and infratentorial, are associated with poor HRQoL in survivors. Infratentorial and thalamic involvement by ICH are associated with the greatest risk of death, and internal capsule lesions with the greatest residual disability. It is well-recognized that infratentorial location is a poor prognostic factor. To this, we can now add deep, posterior supratentorial locations involving the thalamus or posterior limb of internal capsule. These data offer additional practical help for clinicians in assessing patients with ICH and counseling patients and families, as well as in planning rehabilitation and developing individualized pathways of care.

**AUTHOR CONTRIBUTIONS**

C. Delcourt, S. Sato, R.A.S. Salman, and C.S. Anderson contributed to the concept and rationale for the study. S. Sato, D. Zheng, and H. Arima contributed to data analysis. C. Delcourt, S. Sato, E.C. Sandset, H. Arima, and C.S. Anderson contributed to the interpretation of the results. All authors participated in the drafting and approval of the final manuscript and take responsibility for the content and interpretation of this article.

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**Table 5** Multivariable logistic regression analyses for associations between the most common entire ICH (encompassing one or multiple sites) and health-related quality of life measured by the 5-dimension European Quality of Life scale, by utility score (≤0.7 vs >0.7) and dimension (some/moderate or severe problems vs no problem)

<table>
<thead>
<tr>
<th></th>
<th>Utility score</th>
<th>Mobility</th>
<th>Self-care</th>
<th>Usual activity</th>
<th>Pain/discomfort</th>
<th>Anxiety/depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.81 0.90-3.62</td>
<td>1.42 0.74-2.69</td>
<td>1.39 1.04-1.88</td>
<td>1.76 1.05-2.95</td>
<td>1.52 0.99-2.34</td>
<td>1.09 0.54-2.21</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.14 0.56-2.31</td>
<td>0.65 0.29-1.42</td>
<td>0.95 0.49-1.84</td>
<td>0.71 0.39-1.39</td>
<td>0.60 0.27-1.30</td>
<td>0.59 0.28-1.25</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>1.28 0.58-2.89</td>
<td>0.81 0.36-1.81</td>
<td>0.87 0.44-1.77</td>
<td>0.69 0.35-1.39</td>
<td>0.48 0.21-1.09</td>
<td>0.54 0.26-1.13</td>
</tr>
<tr>
<td>Lobar</td>
<td>1.30 0.60-2.72</td>
<td>0.90 0.40-1.92</td>
<td>0.99 0.47-2.12</td>
<td>0.71 0.36-1.42</td>
<td>0.62 0.29-1.31</td>
<td>0.78 0.37-1.64</td>
</tr>
<tr>
<td>Thalamus and posterior limb of internal capsule</td>
<td>0.94 0.47-1.91</td>
<td>0.77 0.37-1.64</td>
<td>0.61 0.29-1.28</td>
<td>0.71 0.36-1.42</td>
<td>0.61 0.29-1.31</td>
<td>0.79 0.38-1.68</td>
</tr>
<tr>
<td>Putamen/globus pallidus and posterior limb of internal capsule</td>
<td>1.09 0.44-2.70</td>
<td>0.74 0.33-1.66</td>
<td>0.86 0.40-1.85</td>
<td>0.81 0.39-1.70</td>
<td>0.62 0.28-1.30</td>
<td>0.65 0.30-1.40</td>
</tr>
<tr>
<td>Putamen/globus pallidus and external capsule</td>
<td>0.60 0.27-1.41</td>
<td>0.43 0.19-0.96</td>
<td>0.73 0.34-1.58</td>
<td>0.58 0.26-1.12</td>
<td>0.48 0.21-1.06</td>
<td>0.50 0.24-1.06</td>
</tr>
<tr>
<td>Putamen/globus pallidus, posterior limb of internal capsule and external capsule</td>
<td>0.95 0.40-2.26</td>
<td>0.75 0.32-1.76</td>
<td>0.93 0.40-2.12</td>
<td>0.72 0.35-1.50</td>
<td>0.60 0.27-1.29</td>
<td>0.69 0.32-1.47</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; No. = number of cases by intracerebral hemorrhage location; OR = odds ratio. Multivariable models were adjusted for age, female sex, China region, history of ischemic stroke and diabetes, medication history of antihypertensives, antithrombotics, and lipid-lowering agents, NIH Stroke Scale score (≤11 vs >11), systolic blood pressure, onset to CT time (log-transformed), baseline hematoma volume (log-transformed), caudate head, thalamus, putamen/globus pallidus, external capsule, anterior and posterior limbs of internal capsule, lobar, infratentorial, and intraventricular extension of hematoma, ICH laterality, randomization to intensive blood pressure-lowering management policy, and proxy responders. The c statistics for the models of utility score, mobility, self-care, usual activity, pain/discomfort, and anxiety/depression were 0.79, 0.78, 0.82, 0.66, and 0.89, respectively.

* p ≤ 0.05

\( p < 0.01 \)

\( p < 0.001 \)
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Intracerebral hemorrhage location and outcome among INTERACT2 participants
Candice Delcourt, Shoichiro Sato, Shihong Zhang, et al.
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