A cute intracerebral hemorrhage (ICH) is a common cause for symptomatic seizures. In the recent prospective studies, symptomatic seizures among patients with ICH have ranged from 5% to 14% within the first days after event.1–3 During 2 years of follow-up, 8% to 10% of ICH survivors develop additional late seizures (LS).4,5 

Early seizures are thought to result from structural changes producing acute disruption of brain integrity, metabolic homeostasis, and transient depolarizations, whereas LS relate to neuronal reorganization and formation of epileptogenic foci.6 Because of different predisposing factors, early seizure and LS have diversity in prognosis.7 Several studies have examined the relationship between acute ICH and epileptic seizures with conflicting results possibly because of heterogeneous designs, inconsistent use of terminology, duration of follow-up, or differences in seizure identification and classification. 

LS after ICH occurs relatively commonly and usually necessitates secondary prophylaxis.8 A tool identifying patients with a high risk of seizures would be of benefit, but currently it does not exist. The goals of our study were to (1) describe the frequency of post-ICH seizures and factors associated with these, (2) develop a simple predictive score based on baseline clinical data, and (3) validate the score in an independent prospective ICH cohort.

Methods
This study was conducted at the Department of Neurology, Helsinki University Central Hospital, which has the only neurological emergency room with 24/7 service in a catchment area of 1.5 million inhabitants. We retrospectively analyzed all consecutive primary
ICH patients treated from January 2005 to March 2010 as previously described, including ICH because of structural vascular lesions such as arteriovenous malformations and cavernomas, medication such as anticoagulation, amyloid angiopathy, systemic/other disease such as liver cirrhosis, hypertension, or undetermined causes, but excluding, as per World Health Organization definition, ICH because of tumor, trauma, subarachnoid hemorrhage, or ischemic stroke. Patients with previous ICH were included only if they had a new ICH during the study period. For the purpose of the present analysis, we excluded patients with prior epilepsy. Patients were treated according to published guidelines. The study protocol was considered observational by the internal review boards of the Lille University Hospital and Helsinki University Central Hospital. The databases were declared to the ad hoc commissions protecting personal data. Patient consent for registration was not required, and all consecutive cases were included.

Seizures we defined early seizures as occurring at onset or emerging after onset but within 7 days of ICH onset. Seizures that occurred thereafter were defined as late. Seizures were classified according to suggested descriptors for focal seizures as occurring (1) with observable focal motor or autonomic components only, (2) focal signs with impairment of consciousness, or (3) evolving to a bilateral convulsive seizure with loss of consciousness. Status epilepticus was defined as a seizure or seizures continuing >30 minutes without recovery between episodes. Data about the timing and duration of seizures, the clinical characteristics of the first seizure, and occurrence of status epilepticus were registered as described elsewhere. Seizures had been originally diagnosed as such by neurologists in charge of the patients’ treatment. All patient records from hospitals and primary health care via a province-wide electronic patient record were retrieved and evaluated. A paroxysmal event was not classified as a seizure if it was limited to psychic phenomena, lacked proper differential diagnosis of syncope, or could have been a transient ischemic attack. All seizure events were evaluated by an epileptologist during review of medical records. The surviving patients identified as having symptoms suggestive for univariate associations with LS using the log-rank test, with the continuous variables first dichotomized based on classification regression tree analysis cutoffs; (2) the variables with univariate associations ($P<0.10$) were entered into a multivariable Cox regression model with backward stepwise removal ($P<0.05$); (3) the remaining variables were scored integer points based on their final regression coefficients; (4) discrimination statistics (area under receiver operating characteristic curve, c-statistic) with 95% confidence intervals described how well the total score matched the observed values; (5) external validation was performed in the PITCH cohort. SPSS 20 (IBM Corp, Armonk, NY) was used for the analyses. A 2-sided $P$ value <0.05 was considered significant.

Results

Between January 1, 2005, and March 31, 2010, a total of 1013 primary ICH patients were treated in our hospital. After excluding the 20 patients with a history of seizures or epilepsy before their ICH, we included 993 patients in our analysis (Table 1). Early Seizures An early seizure was noted in 109 patients (11.0%), either at onset (n=48), after onset but within 7 days (n=45), or both (n=16). Sixteen (15%) had focal motor or autonomic signs only, 19 (17%) had focal signs together with impaired consciousness, 57 (52%) had bilateral convulsive seizures, and 17 (16%) progressed to status epilepticus. Of the 16 patients with both onset seizure and another seizure within 7 days, the second clinical presentation was of the same type except in 3 patients: 1 patient with focal complex at onset followed by convulsive seizure the same day, 1 patient with convulsive seizure at onset and focal complex the same day, and 1 patient with convulsive seizures at onset and status epilepticus on day 3. The majority (90%) of early seizures after onset occurred during the first 3 days after ICH (median, 1 day; interquartile range, 1–2 days). Seizures at onset ($P=0.96$) or later within 7 days ($P=0.77$) were not associated with mortality.

Clinical Outcome

We did not have systematic follow-up for functional outcome. All-cause mortality data were recorded for all patients of the province from national mortality statistics. Foreigners and out-of-province patients were lost to mortality and LS follow-up at discharge. All available patient records were tracked in March 2012 for seizures and AED evaluation.

Validation Cohort

The validation cohort was extracted from the prospective Prognosis of InTra-Cerebral Hemorrhage (PITCH) cohort (recruitment November 2004 to April 2009) based in Lille, France. The validation group consisted of 325 prospectively collected patients with spontaneous ICH who survived ≥7 days and did not have seizures before their ICH. Patients were prospectively followed-up for LS 6 months after ICH and then annually.

Statistical Analyses

To test the effect of seizures on all-cause mortality, we used Kaplan–Meier analysis and the log-rank test for early seizures and annualized mortality rates for LS. We derived and validated a simple integer-based prognostic score to estimate the risk of LS after ICH as follows: (1) all the variables in Table 1 were tested for univariate associations with LS using the log-rank test, with the continuous variables first dichotomized based on classification regression tree analysis cutoffs; (2) the variables with univariate associations ($P<0.05$) were entered into a multivariable Cox regression model with backward stepwise removal ($P<0.05$); (3) the remaining variables were scored integer points based on their final regression coefficients; (4) discrimination statistics (area under receiver operating characteristic curve, c-statistic) with 95% confidence intervals described how well the total score matched the observed values; (5) external validation was performed in the PITCH cohort. SPSS 20 (IBM Corp, Armonk, NY) was used for the analyses. A 2-sided $P$ value <0.05 was considered significant.

Other Parameters

All data were retrospectively retrieved from patient charts and databases. All patients were initially seen by a neurologist, with accordingly diligent chart notes. The Glasgow Coma Scale and the National Institutes of Health Stroke Scale were systematically registered for clarifying metabolic conditions that could provoke seizures and other diagnostic tests according to our institutional protocol. We included all subsequent scans after the ICH in our analysis. Any hemorrhage that involved the cerebral cortex was recorded as cortical involvement, even if the origin of the bleeding was in deep structures. Lesion volumes were estimated with the ABC/2 method. Lesion volumes were estimated with the ABC/2 method.
Late Seizures
A total of 229 patients died (n=213) or were lost-to-follow-up (n=16) before 7 days of their ICH. We included the remaining 764 patients in our analysis of LS (Table 1). Median time to first LS, death, or loss to follow-up was 2.7 years (interquartile range, 0.8–4.4). Seventy patients (9.2%) had LS, with median time to LS of 0.5 years (interquartile range, 0.3–1.3). The risk of LS by ICH cause is shown in Table I in the online-only Data Supplement. The cumulative risk of LS among survivors was 7.1% at 1 year after ICH, 10.0% at 2 years, 10.2% at 3 years, 11.0% at 4 years, and 11.8% at 5 years. The annualized mortality rate was 10.4% without LS (220 deaths during 2113 person-years of observation) and 9.1% after LS (18 deaths during 197 person-years of observation).

A LS occurred in 29 (27%) of the patients with early seizures: in 15 (31%) after onset seizures only, 10 (22%) after early seizures occurring after onset, and 4 (25%) when the patient had both onset and another early seizure. Ten of the patients who had a LS after an early seizure were on AEDs at the time of their LS.

Twenty LS patients (29%) had focal motor or autonomic signs only, 20 (29%) had focal signs together with impaired consciousness, 30 (43%) had bilateral convulsive seizures, and 11 (16%) progressed to status epilepticus.

Sixty-four patients (91%) received AED after their LS. Of the total 70 LS patients, 39 (56%) became seizure free for ≥2 years during follow-up, of which 4 without any AED, and 25 on monotherapy.

CAVE Score for Estimating Risk of LS
Several variables were associated with LS in univariate analysis (Table 2). In multivariable analysis (Table II in the online-only Data Supplement), only cortical involvement, younger age (<65 years), larger ICH volume at baseline (>10 mL), and early seizures within 7 days of ICH were associated with development of LS, with coefficients ranging from 0.8 to 1.5 and all rounded to 1. The CAVE score (0–4 points) consists of cortical involvement of ICH (1 point), age <65 years (1 point), volume >10 (1 point), and early seizure within 7 days of ICH (1 point). The corresponding risk of LS during follow-up was 0.6%, 3.6%, 9.8%, 34.8%, and 46.2% for CAVE score points 0 to 4, respectively. The c-statistic was 0.81 (0.76–0.86). Time to first LS after ICH by CAVE score is shown in Figure 1.

The score was validated externally in the ongoing PITCH cohort, median follow-up of 2.2 years (interquartile range, 1.0–4.3) for the present publication. Baseline characteristics of the validation cohort are outlined in Table 1. LS occurred in 31 of 325 patients (9.5%) during follow-up, the risk being 3.1%, 5.0%, 15.8%, 13.5%, and 37.5% for CAVE score points 0 to 4, respectively. LSs by CAVE score in both the derivation and the validation cohorts are shown in Figure 2. The c-statistic in the validation cohort was 0.69 (0.59–0.78). The sensitivity, specificity, positive and negative predictive values,
and likelihood ratios for the combined Helsinki ICH Study and PITCH cohorts at various dichotomies of the CAVE score are provided in Table III in the online-only Data Supplement.

Discussion

The main findings of our study are as follows: (1) LS occurred more frequently in younger patients, with larger ICH, when the ICH involves the cortex, and after early seizures; and (2) a simple score composed of these variables could be used to stratify the risk of LS after ICH.

Cumulative risk of LS was 7.1% at 1 year after ICH and 11.8% at 5 years. This is in line with earlier reports although comparisons between studies are difficult because of different patient populations, seizure criteria, and follow-up.
Figure 2. Proportion of patients developing late seizures (LSs) during follow-up in Helsinki (n=764) and Lille (n=325) intracerebral hemorrhage series per CAVE score points 0 to 4. Numbers below score are patients with LS and total number of patients with that score in Helsinki and then in Lille.

Early seizures occur mainly within 3 days of ICH onset, supporting the recommendations to monitor ICH patients in acute stroke or intensive care units during the acute stage.11,16 Prior studies have explored the relationship between younger age and seizures.1,21–23 Despite the different design of these studies (mixed population of hemorrhagic and ischemic stroke), age below 65 years was revealed as a factor associated with seizures after ICH. Recently presented data on patient populations similar to ours also demonstrated an association of younger age with seizures.3,23,24 This association might reflect the higher survival probability of younger ICH patients. Differences in the clinical manifestation of epilepsy in elderly and younger adults can lead to underestimation of epilepsy incidence in older people. Convulsive seizures may become less frequent, and clinical seizure manifestations may be more difficult to recognize in the elderly.23

Several previous studies,3,4,19,20,24,26 in line with our results, reported that cortical and lobar ICH represent highly epileptogenic lesions. Electrophysiological studies showed greater probability of spontaneous synaptic events and increased excitability in response to synaptic stimulation in neurons adjacent to cortical lesion compared with those surrounding glia. Hemosiderin deposits have been discussed repeatedly as potential epileptogenic triggers in patients with focal epilepsy due to ICH. Data from a recent study suggest blood–brain barrier dysfunction and accumulation of albumin within astrocytes as new pathological features potentially associated with the epileptogenic mechanism of vascular lesions.27

In contrast to previous series,3,28 we found early seizures to be associated with the risk of developing LS. This discrepancy could be because of our larger sample size (n=764) compared with the 2 previous studies (n=12328 and n=325).5 In the study by Rossi et al.,5 early seizures were more common in patients who developed LS (26%) compared with those who did not (15%), although not statistically significant (P=0.10). In ischemic stroke, early seizures are associated with LS.15,29 Early epileptiformic activity could increase the metabolic demand in a hypoxic tissue causing secondary brain damage and gliotic scarring. The propensity to develop seizures is also likely to be dependent on individual neuronal characteristics, regardless of the type of brain injury.5 Our findings agree with previous studies on larger ICH volume being predictive of LS.23,26 It is reasonable that more extensive neuronal damage associates with higher risk of epileptogenesis.

A tool identifying patients at a high risk of post-ICH epilepsy would be of benefit. One previous study has tried to develop such a tool.30 Strzelczyk et al.5 evaluated 264 consecutive ischemic and hemorrhagic stroke patients and established an epilepsy risk score based on 10 items, which included localization, persisting neurological deficit, stroke subtype, diagnosis of vascular encephalopathy, and early- and late-onset seizures. However, that study included both patients with ischemic stroke and ICH although the underlying mechanisms for these conditions are different. Also, the numbers were small, the derivation did not include multivariable analysis, the predictive model has not been validated, and the score is difficult to use in clinical practice. On the contrary, our CAVE score is easy to remember and calculate, is based on 4 variables readily available soon after the ICH, shows an almost linear risk increase, and has been validated in an independent prospective ICH cohort.

We acknowledge some limitations of our study. First, compared with the derivation cohort c-statistic of 0.81 (0.76–0.86), the validation cohort c-statistic was relatively low at 0.69 and had wide confidence intervals at 0.59 to 0.78. This uncertainty around the validation result is because of small numbers, and further validation in other cohorts is warranted. Second, our study is retrospective. Registering seizure events retrospectively is prone to misdiagnosis and underdiagnosis, although medical reports were collected extensively. However, the score we derived was validated in the prospectively collected PITCH cohort, which had an almost identical overall LS frequency (9.2% versus 9.5%). Third, subclinical seizures may have been missed because electroencephalographic monitoring was not available in most patients. The impact of subclinical seizures on outcome is not known.28 Fourth, our analysis is based on relatively small numbers. Even among the 1000 patients, there were only 70 LS, with a risk of overmodeling. However, the variables that remained in the CAVE score were all with multivariable P<0.005, remaining significant after any Bonferroni correction, and most importantly are intuitive and clinically feasible. Finally, although our follow-up was longer than in previous studies, we still underestimate the incidence of life-time LS after ICH.

Observational studies have provided conflicting results about the value of primary seizure prophylaxis in ICH.31,32 Only 1 small single-center randomized controlled trial has been reported (n=72) comparing immediate valproic acid for 1 month with placebo and demonstrated a nonsignificant decrease in early seizures (1/36 versus 4/36; P=0.4) but no effect on further seizures during a follow-up of 1 year.33 However, patients who develop LS after ICH run a high risk of seizure recurrence, and if antiepileptic medication is not started after LS, >90% can expect further seizures.4,34–36 Although not proven in randomized controlled trials, guidelines recommend antiepileptic medication after seizures in patients with ICH.11,16,37

Conclusions
Our study is the largest observational series on ICH seizures reported to date. The CAVE score we describe here may help clinicians in estimating the risk of LSs in individual patients, preferably after further validation to establish generalizability. However, only 15% of patients with ICH have the highest risk CAVE scores of 3 to 4; even in these patients, the risk
is <50% for several years, and there is no trial evidence that medication would prevent the LSs after ICH. Therefore, at present, the score cannot be used for treatment decisions. The best use of our score would be in selecting patients for a prospective randomized trial on the efficacy of antiepileptogenic treatment in ICH.

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Disclosures
Dr Roivainen has received speaker’s fees from UCB Pharma and has been a member of an advisory board for Eisai. The other authors report no conflicts.

References
The CAVE Score for Predicting Late Seizures After Intracerebral Hemorrhage
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SUPPLEMENTAL MATERIAL.
Haapaniemi et al. The CAVE Score for Predicting Late Seizures after Intracerebral Hemorrhage

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Table I. Late seizures by etiology of intracerebral hemorrhage.

<table>
<thead>
<tr>
<th>SMASH-U etiology</th>
<th>Patients with late seizures n=70/764 (9%)</th>
<th>Univariate hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural vascular lesion</td>
<td>9/47 (19%)</td>
<td>1.82 (0.80-4.11)</td>
</tr>
<tr>
<td>Medication</td>
<td>5/75 (7%)</td>
<td>0.79 (0.29-2.15)</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>21/175 (12%)</td>
<td>1.36 (0.71-2.60)</td>
</tr>
<tr>
<td>Systemic/Other</td>
<td>10/33 (30%)</td>
<td>3.89 (1.76-8.59)</td>
</tr>
<tr>
<td>Hypertensive angiopathy</td>
<td>9/267 (3%)</td>
<td>0.36 (0.16-0.81)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>16/167 (10%)</td>
<td>Reference category</td>
</tr>
</tbody>
</table>

Table II. Cox regression model used to derive the CAVE score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient</th>
<th>Standard Error</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial hemorrhage</td>
<td>-0.85</td>
<td>0.74</td>
<td>0.25</td>
<td>0.43 (0.10-1.84)</td>
</tr>
<tr>
<td>GCS &lt;13</td>
<td>0.39</td>
<td>0.26</td>
<td>0.15</td>
<td>1.47 (0.88-2.47)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>-0.33</td>
<td>0.25</td>
<td>0.18</td>
<td>0.72 (0.44-1.17)</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>0.52</td>
<td>0.27</td>
<td>0.06</td>
<td>1.68 (0.98-2.86)</td>
</tr>
<tr>
<td>Cortical involvement</td>
<td>0.83</td>
<td>0.28</td>
<td>0.003</td>
<td>2.29 (1.31-3.99)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.88</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>2.41 (1.43-4.05)</td>
</tr>
<tr>
<td>Volume of ICH &gt;10 mL</td>
<td>1.02</td>
<td>0.25</td>
<td>&lt;0.001</td>
<td>2.79 (1.69-4.59)</td>
</tr>
<tr>
<td>Early seizure</td>
<td>1.50</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>4.50 (2.68-7.54)</td>
</tr>
</tbody>
</table>

All variables with univariate association with late seizures were entered into the Cox model. Continuous variables were first dichotomized using classification regression tree analysis cutoffs: Age <65, GCS <13, and Volume <10 mL. Variables were removed stepwise (P<0.05), leaving the four CAVE variables marked in bold, all rounded to 1 point for the score.

Table III. CAVE score accuracy with various dichotomies for predicting late seizures after intracerebral haemorrhage.

<table>
<thead>
<tr>
<th>CAVE 1-4</th>
<th>CAVE 2-4</th>
<th>CAVE 3-4</th>
<th>CAVE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.97 (0.91-0.99)</td>
<td>0.81 (0.72-0.88)</td>
<td>0.46 (0.36-0.56)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.23 (0.20-0.26)</td>
<td>0.62 (0.59-0.65)</td>
<td>0.89 (0.87-0.91)</td>
</tr>
<tr>
<td>PPV</td>
<td>0.11 (0.09-0.14)</td>
<td>0.18 (0.14-0.22)</td>
<td>0.31 (0.24-0.39)</td>
</tr>
<tr>
<td>NPV</td>
<td>0.99 (0.96-1.00)</td>
<td>0.97 (0.95-0.98)</td>
<td>0.94 (0.92-0.96)</td>
</tr>
<tr>
<td>LR</td>
<td>1.26 (1.20-1.32)</td>
<td>2.12 (1.88-2.40)</td>
<td>4.33 (3.27-5.73)</td>
</tr>
</tbody>
</table>

Data with 95% confidence intervals are for the combined HICHS and PITCH cohorts (n=1089). PPV indicates positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Supplemental References