Prognostic Factors for Cognitive Decline After Intracerebral Hemorrhage

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Background and Purpose—Stroke and dementia are closely related, but no prospective study ever focused on poststroke cognitive decline in patients with intracerebral hemorrhage (ICH). We aimed to determine prognostic factors for cognitive decline in patients with ICH.

Methods—We prospectively included 167 consecutive ICH survivors without preexisting dementia from the Prognosis of Intra-Cerebral Hemorrhage (PITCH) cohort. Median follow-up was 4 years (interquartile range, 2.3–5.4). We explored factors associated with cognitive decline using linear mixed models. Cognitive decline was determined based on repeated mini-mental state examination. We investigated each prognostic factor separately in univariate models. Next, we constructed clinical and radiological multivariable models. In a sensitivity analysis, we excluded patients with preexisting cognitive impairment.

Results—Median age was 64 (interquartile range, 53–75) years, 69 (41%) patients were women, and median mini-mental state examination at 6 months was 27 (interquartile range, 23–29). Overall, 37% of the patients declined during follow-up. Factors associated with cognitive decline in univariate analyses were previous stroke or transient ischemic attack, preexisting cognitive impairment, microbleed presence, severity of white matter hyperintensities, and severity of cortical atrophy. In multivariable analyses, previous stroke or transient ischemic attack (β [SE], −0.55 [0.23]; P<0.05), preexisting cognitive impairment (β [SE], −0.56 [0.25]; P<0.01), and severity of cortical atrophy (β [SE], −0.50 [0.19]; P<0.01) remained independent prognostic factors. In patients without preexisting cognitive impairment (n=139), severity of cortical atrophy (β [SE], −0.38 [0.17]; P<0.05) was the only prognostic factor for future cognitive decline.

Conclusions—Prognostic factors for cognitive decline after ICH are already present when ICH occurs, suggesting a process of ongoing cognitive impairment instead of new-onset decline induced by the ICH itself. (Stroke. 2015;46:2773-2778. DOI: 10.1161/STROKEAHA.115.010200.)

Key Words: cerebral hemorrhage ■ dementia ■ ischemic attack, transient ■ mild cognitive impairment ■ stroke
Methods

Patients
We included patients from the Prognosis of Intra-Cerebral Hemorrhage (PITCH) cohort, which is an ongoing observational study.11 All adults admitted in the Lille University Hospital with parenchymal hemorrhage on computed tomography were included in this cohort (November 2004–April 2009). Exclusion criteria were pure intraventricular hemorrhages; ICH resulting from intracranial vascular malformation, intracranial venous thrombosis, head trauma or tumor; hemorrhagic transformation within an infarct; or referral from other hospitals. This study focuses on cognitive decline during follow-up. Therefore, we included patients alive at first follow-up after discharge, that is, 6 months after ICH (Figure 1). Based on the French translation of the short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),12 we excluded patients who were regarded to have preexisting dementia (score ≥64, in line with previous recommendations13).

We prospectively collected the following demographic characteristics: age, sex, and educational level (≤8 versus >8 years). We determined the presence of vascular risk factors according to the medical history (definitions were previously published15). We recorded history of previous stroke or transient ischemic attack (TIA) and atrial fibrillation. We determined preexisting level of cognition based on the short version of the IQCODE (scores ≥53: preexisting cognitive impairment, in line with previous recommendations15). Preexisting level of dependency was determined with the modified Rankin scale (score ≥2: dependent before ICH).14 The presence of depressive symptoms at 6 months was measured using the Montgomery and Asberg depression rating scale (MADRS; score ≥7: presence of depressive symptoms).15,16

The study protocol was considered as observational by the internal review board of the Lille University Hospital. The design of the PITCH cohort is in line with the statement for strengthening the reporting of observational studies in epidemiology.17 The database was declared to the ad hoc commission protecting personal data.

Radiological Assessment
Brain computed tomographic scans were performed at admission in all patients. Computed tomographic scans were reviewed by a senior stroke specialist, blinded to clinical data. The location of the ICH was considered as (1) lobar (frontal, temporal, parietal, and occipital; when the origin appeared to be in the cerebral hemispheres superficial to the deep gray matter structures); (2) nonlobar (deep; when the hemorrhage originated from lenticular or caudate nucleus, thalamus, internal or external capsule, or in the posterior fossa and when the hemorrhage originated from the brain stem or cerebellum), or (3) undetermined in cases of large ICH. The volume of the hemorrhage was calculated according to the validated AxBxC/2 method.18

Patients without contraindications underwent a brain magnetic resonance imaging (MRI) soon after admission on a 1.5T scanner. The MRI protocol included axial T1-weighted, T2-weighted, diffusion, fluid-attenuated inversion recovery, and T2*gradient echo-weighted sequences. All images were assessed by a senior stroke specialist blinded to clinical data. To assess global cortical atrophy, we used a 4-point rating scale,19 which was dichotomized into absent (0–1) or present (2–3). White matter hyperintensities were assessed using the Fazekas scale (0–3)20 and dichotomized into absent (0–1) or present (2–3). The term lacune was used to describe scars of lacunar infarctions and referred to deep, subcortical, or pontine ovoid lesions (3–15 mm) with cerebrospinal fluid-like signal with or without a hyperintense fluid-attenuated inversion recovery border.21 Lacunes were scored as absent or present. Brain microbleeds were defined as small round foci of hypointense signal, ≤10 mm in brain parenchyma on T2* gradient echo-weighted images and rated using the brain observer microbleed scale.22 Brain microbleed presence was defined as the presence of ≥1 brain microbleeds. Microbleed location was determined as strictly lobar versus any nonlobar microbleed.

Follow-Up
Patients were invited to be followed up at 6, 12 months, and annually thereafter. At each visit, the occurrence of new stroke or TIA was recorded and analyzed as a binary prognostic factor (no/yes). For this study, we took the date of last available mini-mental state examination (MMSE) as end point of the follow-up; only events occurring before this end point were included in the study.

Evaluation of Cognitive Decline
Cognitive status was evaluated by the administration of the French validated tool MMS,23 (will be referred to as MMSE) at each follow-up visit. The MMSE was administered by certified neurologists with 5 to 20 years of experience. To be included in this study, patients had to have at least 2 MMSE scores. Because of the initial

Figure 1. Overview of patient selection. ICH indicates intracerebral hemorrhage; and MMSE, mini-mental state examination.
Cognitive/functional status

Medical history (%)

Previous stroke or TIA

Dependent before ICH (modified Rankin≥2)

ICH characteristics

ICH volume, mL*

Anatomic distribution‡ (%)

MRI data at baseline (%)

Brain microbleed presence

Strictly lobar brain microbleeds

White matter hyperintensity severity (Fazekas ≥2)

Lacune presence

Global cortical atrophy severity (score ≥2)

Data are presented as number of patients with variable present (%) or median* (interquartile range). χ² test and Mann–Whitney U test are performed, respectively. Missing data for patients with cognitive data available: education, 6/167; IQCODE, 7/167; MADRS, 21/167; ICH location, 6/167; brain microbleeds, 28/167; and white matter hyperintensities, lacunes, and global cortical atrophy, 26/167. ICH indicates intracerebral hemorrhage; IQCODE, Informant Questionnaire on Cognitive Decline in Elderly; MADRS, Montgomery and Asberg Depression Rating Scale; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

‡Anatomic distribution only refers to unique ICH (vs multiple).

§P<0.01.

severity of ICH patients, reliable MMSE could not be obtained at admission for the acute ICH. Therefore, we considered the MMSE measured at 6 months as an adequate measure of cognitive status after ICH.

Results

Overall Description

We included 560 patients with spontaneous ICH in the PITCH cohort. Two hundred ninety-six patients died within the first 6 months and 31 patients had preexisting dementia; they did not meet inclusion criteria for the present analysis. Of the remaining 233 patients, 167 met our inclusion criteria with at least 2 MMSE scores available (Figure 1). Patients without cognitive data available were older (P<0.05), had more severe white matter hyperintensities (P<0.01), and more severe cortical atrophy (P<0.05) than patients with cognitive follow-up available (Table 1).

Characteristics of the Cohort

Among the 167 patients (median age, 64 years; interquartile range [IQR], 53–75; 69 [41%] women), the median baseline MMSE was 27 (IQR, 23–29). The data set included 735 MMSE scores, with a median of 5 MMSE scores per patient (IQR, 3–5). Median duration of follow-up was 4.0 years (IQR, 2.3–5.4). In total, 62 patients (37%) showed cognitive decline

Data Analysis

We used SPSS 20.0 to perform statistical analysis. To determine whether patients with cognitive data available during follow-up differed from patients for whom cognitive data were not available, we compared the main baseline characteristics between those 2 groups, using χ² test for categorical variables and Mann–Whitney U test for continuous variables.

We used linear mixed models to assess the predictive value of demographic variables (age [dichotomized by the median], sex, and education), vascular risk factors (history of hypertension, diabetes mellitus, hypercholesterolemia, current smoking, and excessive alcohol consumption), medical history (previous stroke or TIA and atrial fibrillation), preexisting cognitive and functional status (IQCODE, modified Rankin scale), presence of depressive symptoms (MADRS), ICH characteristics (volume in mL [dichotomized by median], location, and multiple hemorrhages), MRI data (presence and location of microbleeds, severity of white matter hyperintensities, presence of lacunes, and severity of cortical atrophy), and the occurrence of new stroke or TIA during follow-up. Outcome was cognitive decline as measured with MMSE.

A linear mixed model has increased statistical power because it accounts for within-person correlations over time, allows different numbers of assessments, and accounts for varying time intervals between assessments. All assessments, including MMSE at 6 months, were taken into account. A random intercept and random slope with time (in years) were assumed, meaning that the model accounted for individual variation of change in MMSE over time.

First, in line with our statistical plan, we performed univariate linear mixed models for each prognostic factor. These models included terms for the variable of interest, time, and the interaction between the variable and time; MMSE was the dependent variable. Next, we applied a stepwise method and included variables with a univariate P value <0.1 in multivariable linear mixed models. We constructed 2 multivariable models, 1 clinical and 1 radiological, not only to investigate both the importance of patient characteristics but also to explore potential explanatory anatomic biomarkers. Based on the multivariable results, we performed a post hoc sensitivity analysis in patients without preexisting cognitive impairment at the time of ICH onset (n=139). For this subgroup, few variables had a univariate P value <0.1, and we therefore built only 1 multivariable model (including both clinical and radiological variables). In addition, we performed a preplanned subgroup analysis to investigate whether prognostic factors for cognitive decline differed according to ICH location. We therefore repeated the analysis stratifying patients according to ICH location (lobar or nonlobar).
In this study, we chose to focus on cognitive decline instead of dementia, as cognitive decline includes all consequences of stroke, even if criteria for dementia are not met. Another important prognostic factor for subsequent decline in the univariate model, we hypothesized that prognostic factors might be different in the subset of patients without preexisting cognitive impairment. Therefore, we repeated the analyses excluding patients with preexisting cognitive impairment. Results of univariate analyses are presented in Table 2. In the multivariable model (including previous stroke or TIA, severity of cortical atrophy, recurrent stroke or TIA, age, and sex), severity of cortical atrophy was the only prognostic factor for cognitive decline (β[SE], −0.38[0.17]; P<0.05).

**Table 2. Prognostic Factors for Cognitive Decline for the Entire Cohort (n=167) and for Patients Without Preexisting Cognitive Impairment at the Time of ICH Onset (n=139)**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Overall Cohort (n=167)</th>
<th>Patients Without Preexisting Cognitive Impairment (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>−0.24 (0.11)†</td>
<td>−0.00 (0.10)</td>
</tr>
<tr>
<td>Female sex</td>
<td>−0.29 (0.12)†</td>
<td>−0.04 (0.11)</td>
</tr>
<tr>
<td>Education (≤8 y)</td>
<td>−0.06 (0.11)</td>
<td>0.04 (0.10)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.13 (0.10)</td>
<td>−0.04 (0.09)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.39 (0.23)</td>
<td>−0.13 (0.23)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>−0.03 (0.14)</td>
<td>−0.02 (0.13)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.16 (0.18)</td>
<td>0.20 (0.16)</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>−0.23 (0.14)</td>
<td>−0.05 (0.13)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>−0.50 (0.21)†</td>
<td>−0.42 (0.23)§</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>−0.31 (0.25)</td>
<td>−0.06 (0.28)</td>
</tr>
<tr>
<td>Cognitive/functional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent before ICH (modified Rankin≥2)</td>
<td>−0.06 (0.23)</td>
<td>−0.01 (0.29)</td>
</tr>
<tr>
<td>Cognitive impairment before ICH (IQCODE≥53)</td>
<td>−0.76 (0.22)§</td>
<td>...</td>
</tr>
<tr>
<td>Depression</td>
<td>0.03 (0.16)</td>
<td>0.13 (0.14)</td>
</tr>
<tr>
<td>ICH characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH volume</td>
<td>0.01 (0.11)</td>
<td>0.11 (0.10)</td>
</tr>
<tr>
<td>Lobar location</td>
<td>−0.03 (0.13)</td>
<td>0.06 (0.12)</td>
</tr>
<tr>
<td>Multiple ICHs</td>
<td>−0.34 (0.36)</td>
<td>0.01 (0.36)</td>
</tr>
<tr>
<td>MRI data at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain microbleed presence</td>
<td>−0.24 (0.11)†</td>
<td>−0.06 (0.11)</td>
</tr>
<tr>
<td>Strictly lobar brain microbleeds</td>
<td>−0.28 (0.28)</td>
<td>−0.32 (0.26)</td>
</tr>
<tr>
<td>White matter hyperintensity severity (Fazekas ≥2)</td>
<td>−0.24 (0.11)†</td>
<td>0.00 (0.11)</td>
</tr>
<tr>
<td>Lacune presence</td>
<td>−0.25 (0.14)</td>
<td>0.06 (0.13)</td>
</tr>
<tr>
<td>Global cortical atrophy severity (score ≥2)</td>
<td>−0.48 (0.13)†</td>
<td>−0.28 (0.14)†</td>
</tr>
<tr>
<td>Follow-up data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or TIA during follow-up</td>
<td>−0.38 (0.24)</td>
<td>−0.42 (0.22)§</td>
</tr>
</tbody>
</table>

Data are reported as β(SE). Univariate linear mixed models were used to assess the association between each variable and the rate of cognitive decline as measured with the MMSE. A random intercept and a random slope with time (years) were assumed. The model included terms for each variable, time, and the interaction between each variable and time. ICH indicates intracerebral hemorrhage; MADRS, Montgomery and Asberg depression rating scale; MMSE, mini mental state examination; MRI, magnetic resonance imaging; and TIA, transient ischemic attack.

*Age was dichotomized by the median: ≥65 years for the total cohort and ≥63 years for patients without cognitive decline.
†P<0.05.
‡P=0.06.
§P=0.01.
||ICH volume (mL) was dichotomized by the median volume: ≥6.48 mL for total cohort and ≥6.76 mL for patients without cognitive decline.

**Prognostic Factors for Cognitive Decline in the Overall Study Population**

We used linear mixed models with random intercept and slope to investigate associations for patient characteristics with annual change in MMSE (Table 2; Figure 2).

In the clinical multivariable model (including diabetes mellitus, excessive alcohol consumption, previous stroke or TIA, preexisting cognitive impairment, age, and sex), we found that previous stroke or TIA (β[SE], −0.55[0.23]; P<0.05) and preexisting cognitive impairment (β[SE], −0.56[0.25]; P<0.05) were independently associated with annual decline in MMSE. In the radiological multivariable model (including brain microbleed presence, severity of white matter hyperintensities, lacune presence, severity of cortical atrophy, age, and sex), severity of cortical atrophy was the only prognostic factor for cognitive decline (β[SE], −0.50[0.19]; P<0.05).

**Prognostic Factors for Cognitive Decline in Patients Without Preexisting Cognitive Impairment**

Because preexisting cognitive impairment was the strongest prognostic factor for subsequent decline in the univariable model, we hypothesized that prognostic factors might be different in the subset of patients without preexisting cognitive impairment. Therefore, we repeated the analyses excluding patients with preexisting cognitive impairment. Results of univariate analyses are presented in Table 2. In the multivariable model (including previous stroke or TIA, severity of cortical atrophy, recurrent stroke or TIA, age, and sex), severity of cortical atrophy was the only prognostic factor for cognitive decline (β[SE], −0.38[0.17]; P<0.05).

**Prognostic Factors for Cognitive Decline According to ICH Location**

To evaluate the possible influence of ICH location (lobar or nonlobar), we performed an additional analysis stratifying patients according to ICH location. Prognostic factors did not differ for patients with lobar (n=46) or nonlobar ICH (n=88; Table I in the online-only Data Supplement).

**Discussion**

In a prospective cohort of 167 consecutive ICH survivors, we found that 1 of 3 patients exhibited cognitive decline during a median follow-up of 4 years. Preexisting cognitive impairment, severity of cortical atrophy, and previous stroke or TIA were important prognostic factors for cognitive decline after an ICH, suggesting that prognostic factors are already present before ICH occurs.

This is the first prospective study in a large cohort of consecutive ICH patients that focused on cognitive decline over time using systematic, standardized cognitive evaluations. In this study, we chose to focus on cognitive decline instead of dementia, as cognitive decline includes all consequences of stroke, even if criteria for dementia are not met. Another strength is the use of linear mixed models. These models take during follow-up, with a median decline of −1 MMSE points per year (IQR, −2 to −0.4).
into account all available data points, allowing patients to have variable numbers of follow-up measurements. An advantage of the PITCH cohort is its hospital-based recruitment enabling a large sample size with detailed and standardized data collection, including MRI investigations. Moreover, we previously showed that the baseline patient characteristics are comparable with a population-based recruitment\textsuperscript{11} reassuring the external validity of the PITCH cohort.\textsuperscript{17} However, the observational and longitudinal design in a clinical setting has limitations because this may result in a nonrandom loss to follow-up.

One of the limitations is the use of the MMSE as outcome measure. The MMSE is a rather crude measure of cognition and may lack sensitivity to vascular cognitive impairment. Nevertheless, comparisons with the Montreal cognitive assessment still show acceptable validity.\textsuperscript{24,25} Moreover, the MMSE is a generally widely accepted test for the evaluation of cognition in elderly patients and is easily obtainable, thus maximizing the number of patients with available data. Patients with $<2$ MMSE scores available, for instance because of aphasia, appeared to be more severely affected. Therefore, we may have underestimated the weight of cognitive decline in our ICH cohort. A recent Cochrane review\textsuperscript{26} suggests that an (average) IQCODE cutoff $\approx 3.3$ should be used to screen for dementia. However, the PITCH cohort was designed in 2003 when recommendations on the IQCODE suggested a cutoff of 4.0.\textsuperscript{12} Although this may have resulted in an underestimation of the prevalence of preexisting dementia, in an additional analysis, we applied the more stringent criteria recommended by the recent Cochrane review\textsuperscript{26} by excluding patients with preexisting cognitive impairment.

We found that preexisting cognitive impairment and the presence of severe cortical atrophy at baseline (ie, when ICH occurred) were strong prognostic factors for subsequent cognitive decline. Preexisting cognitive impairment has been identified as one of the strongest prognostic factors of cognitive impairment\textsuperscript{6} or dementia\textsuperscript{5,7,27,28} in heterogeneous stroke populations. Similarly, in several reviews, cortical atrophy has shown strong associations with poststroke dementia.\textsuperscript{23,29} The only previous study investigating cognitive decline after ICH unfortunately did not take these characteristics into account.\textsuperscript{10} We found that prognostic factors for cognitive decline after an ICH were already present when ICH occurs, suggesting a process of ongoing cognitive impairment instead of new-onset decline induced by the ICH itself.\textsuperscript{29} The impact of cortical atrophy is in line with this hypothesis and both cortical atrophy and preexisting cognitive impairment may hint toward an underlying neurodegenerative process.\textsuperscript{2,29,30} Nevertheless, brain atrophy is considered as a feature of small vessel disease as well,\textsuperscript{21} and preexisting cognitive impairment may also result from an ongoing cerebrovascular process.\textsuperscript{31} Despite uncertainty about the underlying process, our results indicate that further cognitive decline may be expected in patients with preexisting cognitive impairment and cortical atrophy.

Patients with history of previous stroke or TIA exhibited a steeper rate of cognitive decline in this study. Previous studies, performed in heterogeneous stroke populations with few ICH patients, showed similar results.\textsuperscript{6,7} In the only previous study on cognitive outcome after ICH, previous stroke did not predict dementia.\textsuperscript{10} This study may have had a limited sample size ($n=78$) and a retrospective design.

Our findings are in line with literature suggesting an interplay between neurodegenerative and vascular pathology in cognitive decline.\textsuperscript{32,33} Our results, however, also show the difficulty in determining the relative contribution of each pathology. Ongoing studies may help disentangling vascular and neurodegenerative pathology in poststroke dementia, for instance by studying the nature of brain atrophy (Study of Factors Influencing Post-Stroke Dementia [STROKDEM], Figure 2).

![Figure 2. Estimated regression lines of mini-mental state examination (MMSE) score by time. A. For patients with and without previous stroke or transient ischemic attack (TIA). B. For patients with and without preexisting cognitive decline. C. For patients with and without global cortical atrophy. D. For patients with lobar and nonlobar intracerebral hemorrhage (ICH).](http://stroke.ahajournals.org/)
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**Disclosures**

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**References**


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