Early neurologic deterioration in intracerebral hemorrhage

Predictors and associated factors

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Abstract—*Objective:* To identify potential predictors of and factors associated with early neurologic deterioration (END) in primary intracerebral hemorrhage (ICH). *Methods:* Two hundred sixty-six patients with spontaneous supratentorial ICH admitted within 12 hours of stroke onset were investigated in a multicenter, prospective study. Sixty-one clinical, biochemical, and neuroimaging variables were registered on admission, and 37 clinical and neuroimaging variables were registered at 48 hours. The volumes of the ICH and peripheral edema on admission and at 48 hours were measured on CT scan. Stroke severity and functional outcome were evaluated with the Canadian Stroke Scale (CSS) and modified Rankin Scale. END was diagnosed when the CSS score decreased ≥1 points between admission and 48 hours. With use of logistic regression analyses, baseline variables that predicted END and factors measured after the early acute phase and associated with END were investigated. *Results:* END occurred in 61 (22.9%) patients. Body temperature of >37.5 °C (odds ratio [OR] 24.5; 95% CI 4.8 to 125), neutrophil count (by 1,000-unit increase; OR 2.1; 95% CI 1.6 to 2.6), and serum fibrinogen levels of >523 mg/dL (OR 5.6; 95% CI 1.9 to 16.2) on admission were independent predictors of END. Among the factors recorded at 48 hours, early ICH growth (OR 4.3; 95% CI 1.3 to 14.5), intraventricular bleeding (OR 2.6; 95% CI 1.4 to 5.0), and highest systolic blood pressure (by 10-unit increase; OR 1.17; 95% CI 1.02 to 1.32) were associated with END in multivariate analyses. *Conclusions:* Clinical and biologic markers of the inflammatory reaction on admission are predictors of subsequent END, whereas early ICH growth, intraventricular bleeding, and high systolic blood pressure within 48 hours are factors associated with END in patients with spontaneous ICH.

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Intracerebral hemorrhage (ICH) constitutes 10 to 15% of all strokes and is associated with poor prognosis.[1,2] Early neurologic deterioration (END) in patients with ICH is generally thought to be due to enlargement of the hemorrhage or development of hydrocephalus, whereas late deterioration is linked to perilesional edema.[3] Among the factors related to the poor prognosis of ICH are the size of the hemorrhage itself, intracranial hypertension with cerebral tissue displacement and herniation, and cellular death that occurs hours or days later in the tissues surrounding the hematoma.[4]

There are a number of prognostic models of mortality and functional outcome after ICH.[4-9] These models usually include criteria related to neurologic condition, various other clinical and laboratory measures, and neuroimaging findings. However, the mechanisms of END in patients with ICH are still poorly understood. We attempted to identify factors that predicted or were associated with END in patients with spontaneous ICH and to evaluate the influence of END on clinical outcome.

Methods. *Design and patients.* A cohort study was conducted in 266 patients with spontaneous supratentorial ICH admitted consecutively to 15 hospitals between May 1999 and April 2001 (see Appendix 1). Inclusion criteria were time from the onset of symptoms to admission of <12 hours (in those with strokes present on awakening, time of onset was taken as the time when the patient was last seen normal) and absence of stupor or coma. Patients with hematoma secondary to head injury, congenital or acquired coagulation abnormalities, or any secondary cause of hemorrhage requiring surgical treatment such as cerebral aneurysm, arteriovenous malformation, or tumor were excluded. The study was approved by the institutional review board of all participating institutions, and informed consent was obtained from the patients or their relatives.

Study development. On arrival in the emergency department, blood pressure and body temperature were recorded and blood samples were taken. Each patient underwent a baseline head CT scan and a neurologic evaluation by a neurologist experienced in using the Canadian Stroke Scale (CSS).[10] The CSS measures level of consciousness (alert = 3, drowsy = 1.5), speech (normal = 1, expressive deficit = 0.5, receptive deficit = 0), orientation (oriented = 1, disoriented or not applicable = 0), facial paresis (none = 0.5, present = 0), and weakness in arm, hand, and leg (none = 1.5, mild = 1, moderate = 0.5, total = 0; scored individually for each item), with a total score ranging from 1.5 (maximum deficit) to 10 (absence of deficit). Patients were admitted to a neurologic ward or acute stroke unit and were managed by a specialized stroke team and nursing staff following established guidelines.[11] Blood pressure and body temperature were measured

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Table 1 *Potential predictors at baseline of END*

Predictor	END, n = 61	Non-END, n = 205	*p*
Age, y	72 ± 8	70 ± 11	0.208
Sex, male	64	53	0.143
Time from onset to inclusion, h	6.1 ± 3.1	6.1 ± 3.2	0.992
CSS score	4.5 (3, 6)	5 (3, 6.5)	0.194
Preceding infection, within 15 d	13.1	3.4	0.008
Inflammatory disease, within 30 d	9.8	2.4	0.020
Fever within previous 15 d	9.8	2.9	0.033
Body temperature, °C	37.3 ± 0.7	36.4 ± 0.5	<0.001
Hemoglobin, mg/dL	14.3 ± 1.7	13.8 ± 1.5	0.034
Leukocyte count, $\times 1{,}000/mm^3$	12.8 ± 3.2	8.6 ± 5.1	<0.001
Neutrophil count, $\times 1{,}000/mm^3$	10.8 ± 2.9	6.3 ± 4.3	<0.001
Plasma fibrinogen, mg/dL*	546 ± 126	396 ± 119	<0.001
ESR 1st h, mm†	39 ± 14	22 ± 19	<0.001
CPK, U/L‡	220 ± 231	151 ± 150	0.043

Numbers in parentheses are quartiles.

* In 56 patients with END and in 178 without END.
† In 53 patients with END and in 163 without END.
‡ In 54 patients with END and in 172 without END.

END = early neurologic deterioration; CSS = Canadian Stroke Scale; ERS = erythrocyte sedimentation rate; CPK = creatine phosphokinase.

every 6 hours in the first 48 hours after admission. Antihypertensive treatment with IV labetalol or captopril was administered in case of systolic blood pressure of >185 mm Hg or diastolic blood pressure of >105 mm Hg. Low-dose subcutaneous heparin was used for the prevention of deep vein thrombosis and pulmonary embolism. Glucose-containing IV solutions or corticosteroids were discouraged. Hyperthermia (>37.5 °C) was controlled by the administration of metamizol or acetaminophen. Intracranial pressure monitoring was performed only in one patient, so the relevance of intracranial hypertension was clinically evaluated by local investigators. Specific treatment given for suspected intracranial hypertension was mannitol in 47 patients, steroids in 3, and hyperventilation in 1. Only two patients were surgically treated within 48 hours after admission. None of the patients was part of a therapeutic clinical trial.

Table 2 *Predictors of END selected by final logistic model*

Predictor	Odds ratio	95% CI	*p*
Age	1.00	0.96–1.06	0.77
Sex, male	1.71	0.60–4.84	0.31
Time from onset to inclusion, h	1.00	0.85–1.19	0.92
CSS score	0.94	0.74–1.18	0.62
Body temperature, >37.5° C	24.5	4.8–125	<0.001
Neutrophil count, $\times 1{,}000/mm^3$	2.08	1.64–2.65	<0.001
Fibrinogen, >523 mg/dL	5.59	1.93–16.2	<0.001

After exclusion of missing covariates, 55 patients with END and 176 patients without END were analyzed. Age, sex, time from onset to inclusion, and CSS score on admission were forced into the logistic model.

END = early neurologic deterioration; CSS = Canadian Stroke Scale.

Stroke severity was assessed by the CSS on admission, at 48 hours, and at 3 months. CSS was scored as 0 when the patient was dead at a particular interval. Stroke functional outcome was evaluated by the modified Rankin Scale (mRS) at 90 days. Patients with an mRS score of ≤2 were considered to have a good outcome, whereas those with an mRS score of >2 were classified in the poor outcome category. This scale also included mortality, because patients who died received the worst possible score (value of 6) in this scale.

END was diagnosed when the CSS score decreased ≥1 points between admission and 48 hours after admission. This difference represents the change with the highest sensitivity, retaining good specificity.[12] Patients who died within the first 48 hours were classified in the END group if they had progressed during the observations that followed after inclusion.

For the purposes of this study, we evaluated the cranial CT performed at baseline and at 48 hours. CT scans were performed with a matrix of 512 × 512 and with a slice thickness of 8 to 10 mm. All CT scans were read by a single evaluator who was blinded to the clinical and biochemical data. ICH volumes were calculated on the radiographic plate by using the formula $0.5 \times a \times b \times c$ (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of 10-mm slices containing hemorrhage). The ICH topography was classified as lobar when it affected predominantly the cortical or subcortical white matter of the cerebral lobes or as deep when it was limited to the internal capsule, the basal ganglia, or the thalamus. The presence of intraventricular extension of the hematoma was recorded, but its volume was not measured. Neither the presence of associated subarachnoid hemorrhage nor the development of hydrocephalus after admission was evaluated in this study. The volume of the ICH plus that of the zone of peripheral hypodensity was determined using the same volumetric method described above; the absolute volume of the hypodensity was calculated by subtracting the volume of the ICH from that of the total lesion (ICH + peripheral hypodensity). Relative edema volume was calculated according to the following formula: volume of hypodensity × 100/volume of ICH.

ICH growth was calculated as growth ratio using the following formula: final volume − initial volume × 100/initial volume. Prior studies[13] used ICH expansion of >33% as a minimum criterion for determining hematoma growth. For the primary analyses, we used our prospective definition of ICH growth, established as a difference between the second and the initial CT scan higher than 33% in small (<20-mL) ICH and higher than 10% in large (>20-mL) ICH. Secondary analyses were done using the >33% growth definition for all patients.

Statistical analyses. To look for potential predictors of END, we recorded 61 clinical, biochemical, and neuroimaging variables available on admission (see Appendix 2). To investigate factors measured after the early acute phase and potentially associated with END, we registered 37 clinical and neuroimaging variables 48 hours after admission (see Appendix 2). Categorical variables are shown as percentages. Lesion volumes and CSS score are presented as median values (quartiles) and the rest of the continuous variables as means ± SD.

Tests performed were the χ^2 or two-sided Fisher exact tests for categorical variables and the Student *t*-test or the Mann–Whitney test for continuous variables as appropriate (SPSS 10 software, Chicago, IL). Spearman correlation was used to correlate continuous variables. Potential predictors and factors associated with END in the univariate analyses ($p < 0.05$) plus age, gender, time interval from symptom onset to inclusion, and CSS score on admission were tabulated and were then analyzed in two different models by step-up logistic regression (probability of entry $p < 0.05$), taking into account the hospital as a cluster to estimate the possible overdispersion due to the variability among hospitals. In a further logistic model, we investigated whether factors associated with END were also independently associated with poor functional outcome. We tested the linearity of the explanatory variables related to the risk of END prior to performing the logis-

tic models. Variables that showed no linearity were categorized according to epidemiologic criteria (temperature, ≤37.5 or >37.5 °C) and by means of the Robert method (fibrinogen).[14] No interactions were found. Age, sex, time from onset to inclusion, and CSS on admission were forced into all the models. Results were expressed as adjusted odds ratios (ORs) with corresponding 95% CIs. Logistic regression models were built by means of STATA 8 software (College Station, TX).

Results. Two hundred sixty-six patients (55.3% men; mean age 70.7 ± 10.6 years) were studied, 64 (24.1%) of whom had lobar ICH and 202 (75.9%) deep ICH. The lobar hemorrhage locations were parietal (32 patients), frontal (8 patients), temporal (11 patients), and occipital (13 patients). The deep locations were putamen (57 patients), caudate (22 patients), internal capsule (79 patients), and thalamus (44 patients). Intraventricular bleeding was present in 84 patients (31.6%). The suspected etiology of the ICH was hypertensive in 195 patients, amyloid angiopathy in 16, and idiopathic in 55 patients. The mean time from onset of symptoms to baseline CT scan was 6.1 ± 3.2 hours. Median CSS score on admission was 5 (3, 6.5).

END occurred in 61 patients (22.9%). The extent of deterioration was 1 point in 15 patients, 1.5 or 2 points in 25 patients, 2.5 or 3 points in 18 patients, and >3 points in three patients. ICH location and the suspected etiology were similar in patients with END and without END.

Potential predictors of END in the univariate analysis are shown in table 1. END patients had higher hemoglobin, leukocyte and neutrophil count, erythrocyte sedimentation rate, creatine phosphokinase, and plasma fibrinogen levels at baseline than non-END patients. Regarding risk factors, END patients showed higher frequency of history of fever, infection, or inflammation in the days preceding ICH onset. On admission, body temperature was higher in the END group than in the non-END group ($p < 0.0001$). No findings in the initial CT scan (ICH volume, ICH location [lobar or deep], intraventricular bleeding, mass effect, and absolute or relative volume of peripheral hypodensity) were shown as predictors of END on admission. Age, gender, time from symptom onset to inclusion, and stroke severity on admission were similar in both groups. Of all these variables, body temperature of >37.5 °C on admission, neutrophil count, and plasma fibrinogen levels of >523 mg/dL remained significant predictors of END in the final logistic model (table 2). The frequency of patients correctly classified by the model was 90%.

Table 3 shows the clinical characteristics and CT findings associated with END that were registered during the first 48 hours after admission. The second cranial CT was not performed in three patients who died within 48 hours and in 14 patients owing to technical or logistical reasons. The main baseline characteristics and the frequency of END (29.4 vs 22.5%) in the group with missing CT were not different from those of the total group. Early ICH growth occurred in 67 patients (26.9%), in 18 (16.8%) of 107 patients with ICH of ≤20 mL, and in 49 (34.5%) of 142 patients with ICH of >20 mL. Patients with END showed higher body temperature and systolic blood pressure 48 hours after admission. Enlargement of ICH volume between baseline and 48 hours, larger volume of the ICH and of the peripheral hypodensity, and intraventricular extension of bleeding in CT at 48 hours were significantly related to END. Relative edema volume at 48 hours was similar in both groups. Clinical diagnosis of cerebral herniation and the use of osmotic agents were established as a consequence of the END, whereas cardiac complications were considered as parallel adverse events, so these factors were not included in the logistic model. Early ICH growth, intraventricular bleeding, and the highest systolic blood pressure within 48 hours were the only factors independently associated with END in the final logistic model (table 4).

In a secondary analysis, we studied the association of ICH growth of >33% for all patients and END. Early hematoma growth >33% occurred in 18 patients (12.7%) with ICH of >20 mL. ICH growth of >33% for all sizes of ICH

Table 3 *Potential factors obtained at 48 hours associated with END*

Factor	END, n = 61	Non-END, n = 205	*p*
Body temperature 48 h, °C*	37.5 ± 0.7	37.2 ± 0.6	0.003
Systolic BP 48 h, mm Hg*	192 ± 21	179 ± 27	0.001
ICH volume 48 h, mL†	39 (18, 67)	24 (9, 48)	0.014
Early ICH growth†	48.2	20.7	<0.001
Hypodensity volume 48 h, mL†	25 (11, 41)	15 (6, 27)	0.007
Total volume 48 h, mL†	62 (38, 112)	43 (18, 75)	0.010
Intraventricular bleeding 48 h†	46.4	29.5	0.024
Treatment with osmotic agents	42.4	12.8	<0.001
Cerebral herniation	10.2	1.0	0.002
Cardiac arrest	3.4	0	0.049
Cardiac failure	13.6	2.9	0.004

Numbers in parentheses are quartiles.

END = early neurologic deterioration; BP = blood pressure; ICH = intracerebral hemorrhage.

* In 59 patients with END and in 203 without END.
† In 56 patients with END and in 193 without END.

Table 4 *Factors associated with END selected by final logistic model*

Factor	Odds ratio	95% CI	*p*
Age	1.03	0.99–1.07	0.10
Sex, male	1.96	0.88–4.35	0.09
Time from onset to inclusion, h	0.96	0.90–1.03	0.29
CSS score	1.13	0.96–1.32	0.12
Early ICH growth	4.34	1.29–14.5	0.02
Intraventricular bleeding 48 h	2.65	1.40–5.04	<0.01
Systolic BP 48 h, mm Hg, by 10-unit increase	1.17	1.02–1.32	0.03

After exclusion of missing covariates, 56 patients with END and 185 patients without END were analyzed. Age, sex, time from onset to inclusion, and CSS score on admission were forced into the logistic model.

END = early neurologic deterioration; CSS = Canadian Stroke Scale; ICH = intracerebral hemorrhage; BP = blood pressure.

Table 5 *Adjusted odds ratios (95% CI) of poor functional outcome (mRS >2) for factors independently associated with END*

Factor	Odds ratio	95% CI	*p*
Age	1.04	1.00–1.08	0.04
Sex, male	0.35	0.16–0.75	<0.01
Time from onset to inclusion, h	0.99	0.88–1.13	0.95
CSS score	0.47	0.37–0.60	<0.01
Early ICH growth	3.52	1.47–8.40	<0.01
Intraventricular bleeding	4.75	1.94–11.61	<0.01
Systolic BP 48 h, mm Hg, by 10-unit increase	1.12	0.96–1.31	0.13

After exclusion of missing covariates, 130 patients with poor outcome and 92 patients with good outcome were analyzed.

mRS = modified Rankin Scale; END = early neurologic deterioration; CSS = Canadian Stroke Scale; ICH = intracerebral hemorrhage; BP = blood pressure.

at baseline was found in 26.8% of patients with END and in 10.9% of those without END ($p = 0.003$). The adjusted OR of END for ICH growth of >33% was 3.78 (95% CI 1.67 to 8.57).

We explored the relationship between the predictive and associated factors of END. A higher neutrophil count upon admission was found in patients with early hematoma growth ($p = 0.007$) and intraventricular bleeding at 48 hours ($p < 0.001$), whereas increased fibrinogen concentrations were associated with intraventricular bleeding ($p = 0.003$). A slight correlation was found between neutrophil count ($r = 0.185$, $p = 0.003$) or fibrinogen levels ($r = 0.165$, $p = 0.012$) upon admission and the highest systolic blood pressure within 48 hours ($r = 0.311$), whereas the correlations were greater with the percentage of hematoma growth at 48 hours ($r = 0.182$).

During the study period of 3 months, 28 patients were lost to follow-up. The frequency of END and main baseline characteristics (age, gender, time interval from symptoms onset to inclusion, CSS, and ICH volume on admission) in this subgroup were not different from those of the patients who finished the follow-up. Of the 238 patients who completed the study period, 99 (41.6%) showed good functional outcome at 3 months, 81 (34.0%) were dependent (mRS 3 to 5), and 58 (24.4%) had died. Combined mortality and dependency at 90 days were more frequent in patients with END than in those without END (86 vs 50%; $p < 0.001$). END was associated with an eightfold increase in the probability of poor outcome (95% CI 2.7 to 25.5) after adjusting for age, gender, time from onset to inclusion, and stroke severity on admission and taking into account the variability among hospitals. Among the factors independently associated with END, ICH growth and intraventricular bleeding were also associated with poor functional outcome at 3 months (table 5). The odds of poor outcome for the ICH growth using the >33% definition for all patients was 3.14 (95% CI 1.05 to 9.38).

Discussion. END is a common event after stroke, as it occurs in 20 to 40% of patients, and is associated with poor prognosis.[15] Neurologic deterioration in ICH is most likely to occur within the first 48 hours after onset.[3,13] In this prospective multicenter study, END occurred in 22.9% of patients with spontaneous ICH and was associated with an eightfold increase in the odds of poor outcome. The identification of predictors of END may help to design the therapeutic strategies after ICH. In this study, high body temperature, neutrophil count, and plasma fibrinogen on admission were independent predictors of END. These three factors classified correctly 90% of patients with subsequent END.

Increased body temperature shortly after ischemic stroke independently predicts poor outcome,[16] but the influence of hyperthermia on the early clinical course after ICH has not been established. Hyperthermia may be the result of the acute-phase reaction and inflammatory response or may have deleterious effects as occurs shortly after ischemic stroke. Our results suggest an independent effect in the acute phase, but these findings have not been replicated by others.[17,18]

Two laboratory markers of the stress reaction on admission (high neutrophil count and serum fibrinogen levels) also predicted END in our patients with ICH. Fibrinogen levels have been related to early neurologic deterioration, higher mortality, and poor outcome in ischemic stroke,[19] but only few data are available in patients with ICH.[20,21] As it has been demonstrated that fibrinogen increases in response to inflammatory molecules,[22] we hypothesize that fibrinogen levels may reflect the activation of inflammatory mechanisms responsible for tissue damage around the hematoma.

Initial ICH volume was not an independent predictor of END, in contrast with other studies.[3,23,24] Previous works have estimated the critical hemorrhage volume at 50 mL in deep supratentorial ICH[3] and at 60 mL in lobar ICH.[23] Reduced Glasgow Coma Scale on admission has also been reported as a predictor of END, but no other clinical features, including co-morbidities, blood pressure level, or laboratory studies.[23] Our distinct findings probably reflect different studied populations. As we excluded patients with stupor or coma, those who were initially submitted to surgical treatment, and those not admitted to neurologic wards, we focused on patients with less severe ICH in whom early neurologic worsening as a direct effect of the initial intracranial hypertension was less probable. Earlier recognition of the ICH in our series, before it reached the maximal volume, may also explain the different results, as ICH volume was associated with END later on, at 48 hours. Recently, increased relative edema volume within the first 3 hours after symptom onset was identified as a strong predictor of better functional outcome in ICH.[25] Hyperacute edema due to successful hematoma clotting was proposed to explain this finding, but this paradoxical association has not been replicated in our population, neither with the early clinical course nor with the outcome at 3 months (data not shown).

In contrast to the lack of predictive effect of the initial neuroimaging findings, several indicators of the inflammatory response on admission were related to END in univariate and multivariate analy-

ses. We have previously reported the association between high levels of inflammatory molecules within 24 hours of ICH onset and the volume of the delayed perihematoma brain edema measured on days 3 to 4.[26] New preliminary data suggest that inflammatory-mediated endothelial damage is associated with subsequent ICH growth[27] so both mechanisms, subsequent edema and ICH growth as potential causes of END, might be predicted by some inflammatory markers upon admission.

After the early acute phase, several CT findings were associated with END in the univariate analyses. ICH growth evaluated at 48 hours, but not the total ICH volume, was independently associated with a 4.3 odds of END. A similar fourfold increase in the risk of END was found when the >33% growth definition for all patients was used in the analysis. Our results replicate others' that found association between early ICH growth and END in a prospective study.[13] END occurred in 50% of their patients with early ICH growth, a proportion close to that observed in the current series. This finding is important because the frequency of substantial (>33%) ICH growth has been estimated in 36% within the first 24 hours after symptom onset[13] and in 27% within 48 hours following our definition. Accordingly, emergent therapies in ICH are directed to arrest ongoing bleeding and minimize hematoma growth after ICH with the ultra-early administration of hemostatic factors such as factor VIIa.[28] Although no clinical risk factors of ICH growth have been identified,[13] some markers in blood of the endothelial basal lamina disruption, such as metalloproteinase-9 and fibronectin, have been associated with early ICH growth.[27] This mechanism might be mediated by the inflammatory response in the peripheral brain tissue after ICH[26] and that likely results from clotting of intrahematoma blood and thrombin generation.[29,30] Interestingly, a secondary analysis in this study showed a relationship between the markers of inflammation that predicted END and ICH growth, a fact that supports this hypothesis.

Delayed cerebral edema may also lead to END. Although the initial perihematoma hypodensity is not a predictor of poor functional outcome,[25] edema growth that occurs days to weeks after ICH onset may be associated with increased mass effect and neurologic worsening.[29,31] In our study, large absolute volume, but not relative volume, of perilesional edema at 48 hours was associated with END; however, this effect disappeared after adjusting for early ICH growth. This result likely indicates that within the first 2 days after ICH, edema-mediated neurologic worsening may be an epiphenomenon of the ICH growth and clotting. A further point of interest in this study was the independent effect of systolic blood pressure on END. Hypertension in the acute phase of ICH may contribute to the risk of continued hemorrhage and mortality independent of other prognostic factors such as stroke severity and ICH volume.[5,32,33] Despite treatment recommendations in this project, the highest systolic blood pressure (mean 192 mm Hg) within the first 48 hours after admission in the group with END was over the level (180 mm Hg) below which systolic blood pressure should be maintained according to the American Heart Association guidelines.[34] Although these guidelines are not based on randomized trials, our results support a careful control of systolic blood pressure below 180 mm Hg in ICH.

Intraventricular bleeding at 48 hours was associated with a 2.6-fold increase in the risk of END. Intraventricular extension of supratentorial ICH is a powerful risk factor of increased 30-day mortality and poor functional outcome,[9,25,35] although no studies have analyzed its relation with END. These effects are frequently linked to the presence of hydrocephalus, a variable that was not evaluated in this study. We assume that many patients with intraventricular bleeding at baseline were treated surgically and not enrolled in this multicenter study, so this factor was not selected as a predictor of END.

This study has some methodologic limitations because patients were admitted into different hospitals with different neurologic wards and/or stroke units. However, we controlled for a potential bias due to distinct medical care depending on the participating hospital by using a step-up logistic regression analysis with the variable hospital as a cluster. As specialized medical and nursing personnel were taking care of the patients and the same treatment protocols were followed in the different institutions, it is not likely that the CSS scores of the patients were different depending on the facility. A further limitation is that the influence of withdrawal of care during hospitalization and after hospital discharge on END was not evaluated; however, only two patients were surgically treated after inclusion, so differences between patients regarding an aggressive therapeutic support were unlikely.

Despite the acknowledged limitations, this study has identified some predictors and factors associated with END that may be relevant for the management of patients with spontaneous ICH. Factors associated with END were also independently associated with poor functional outcome at 3 months, so early intervention on these factors could have favorable prognostic consequences at long term.

Appendix 1

Participating centers and investigators (numbers of patients studied): Hospital Clínico Universitario, Santiago de Compostela (62): José Castillo, Rogelio Leira; Hospital Universitari Doctor Josep Trueta, Girona (47): Antonio Dávalos, Yolanda Silvia; Hospital Virgen del Rocío, Sevilla (21): Alberto Gil Peralta, Enrique Montes; Hospital Virgen Blanca, León (21): Javier Tejada; Hospital Clinic, Barcelona, (20): Ángel Chamorro, Nicolás Vila; Hospital Arquitecto Marcide, Ferrol (19): Francisco López, José Aldrey; Hospital Clínico, Valencia (17): José Miguel Láinez, Raquel Chamarro; Hospital Provincial, Pontevedra (16): Manuel Seijo Martínez; Hospital de La Princesa, Madrid (13): José Vivancos, Raquel González; Hospital Clínico, Madrid (9): José Egido; Hospital Vall d'Hebrón, Barcelona (8): José Álvarez-Sabín, Joan Montaner; Hospital Gregorio Marañón, Madrid (5): Antonio Gil, Fernando Díaz; Hospital Virgen de la Concha, Zamora (3): José Carlos Gómez; Hospital La Paz, Madrid (3): Exuperio Diez-Tejedor; Hospital Clínico, Zaragoza (2): Enrique Mostacero.

Appendix 2

List of clinical, laboratory, and neuroimaging variables analyzed on admission and at 48 hours

Variables on admission

- Age
- Sex
- Time of onset
- Time delay to study inclusion
- Arterial hypertension
- Alcohol use
- Liver disease
- Renal failure
- Tobacco use
- Diabetes mellitus
- Antiplatelet drug use
- Sympathicomimetic drug use
- Cytostatic drug use
- Illicit drug use
- Hematologic disease
- TIA/cerebral infarction
- Cognitive deterioration
- Preceding infection (within 15 days)
- Inflammatory disease (within 30 days)
- Fever within the previous 15 days
- Coma
- Vomiting
- Seizures
- Body temperature
- SBP
- DBP
- Headache
- Headache location
- Headache characteristics
- CSS
- ICH location
- Ventricular bleeding
- Mass effect
- Perihematoma hypodensity
- ICH volume
- Total volume
- Edema volume
- Leukoaraiosis
- Cerebral atrophy
- Lacunar infarction
- Old lesion on CT scan
- Hematocrit
- Hemoglobin level
- Leukocyte count
- Neutrophil count
- Platelet count
- Fibrinogen level
- Prothrombin time
- Coagulation time
- C-reactive protein
- ESR
- Serum glucose levels
- HDL cholesterol
- LDL cholesterol
- SGOT
- SGPT
- GGTP
- Alkaline phosphatase level
- CPK level
- Intracranial pressure
- Use of osmotic agents

Variables at 48 hours

- Body temperature
- SBP, highest level
- DBP, highest level
- SBP, lowest level
- DBP, lowest level
- Headache
- Headache location
- Headache characteristics
- Dysphagia
- Cardiac arrhythmia
- Cardiac arrest
- Arterial hypotension
- Myocardial infarction
- Cardiac failure
- Trombophlebitis
- Pulmonary embolism
- Pneumonia
- Bronchial secretions
- Gastric ulceration
- GI bleeding
- Allergic reactions
- Urinary tract infection
- Sepsis
- Decubitus ulcer
- SIADH
- Hyperglycemia
- Seizures
- Cerebral infarction
- CSS
- Ventricular bleeding
- Mass effect
- Perihematoma hypodensity
- ICH volume
- Total volume
- Edema volume
- Intracranial hypertension
- Use of osmotic agents

SBP = systolic blood pressure; DBP = diastolic blood pressure; CSS = Canadian Stroke Scale; ICH = intracerebral hemorrhage; ESR = erythrocyte sedimentation rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; GGTP = γ-glutamyl transpeptidase; CPK = creatine phosphokinase; GI = gastrointestinal; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

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