Elderly Age as a Prognostic Marker of 1-year Poor Outcome for Subarachnoid Hemorrhage Patients through Its Interaction with Admission Hydrocephalus

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ABSTRACT

Background: An increasing number of elderly patients are treated for aneurysmal subarachnoid hemorrhage. Given that elderly age is associated with both poor outcome and an increased risk of hydrocephalus, we sought to investigate the interaction between age and hydrocephalus in outcome prediction.

Methods: We enrolled 933 consecutive patients treated for subarachnoid hemorrhage between 2002 and 2010 and followed them for 1 yr after intensive care unit discharge. We first performed stepwise analyses to determine the relationship among neurologic events, elderly age (60 or more yr old), and 1-yr poor outcome (defined as Rankin 4–6). Within the most parsimonious model, we then tested for interaction between admission hydrocephalus and elderly age. Finally, we tested the association between age as a stratified variable and 1-yr poor outcome for each subgroup of patients with neurologic events.

Results: 24.1% (n = 225) of subarachnoid hemorrhage patients were 60 yr old or more and 19.3% (n = 180) had 1-yr poor outcomes. In the most parsimonious model (area under the receiver operating characteristic curve, 0.84; 95% CI: 0.82 to 0.88; $P < 0.001$), elderly age and admission hydrocephalus were two independent predictors for 1-yr outcome ($P < 0.001$ and $P = 0.004$, respectively). Including the significant interaction between age and hydrocephalus ($P = 0.04$) improved the model's outcome prediction ($P = 0.03$), but elderly age was no longer a significant predictor. Finally, stratified age was associated with 1-yr poor outcome for hydrocephalus patients ($P = 0.007$), but not for patients without hydrocephalus ($P = 0.87$).

What We Already Know about This Topic

- An increasing number of elderly patients are treated for aneurysmal subarachnoid hemorrhage
- Although elderly patients are at risk for poor outcome and hydrocephalus in this setting, the interaction between these has not been adequately studied

What This Article Tells Us That Is New

- In nearly 1,000 consecutive patients with aneurysmal subarachnoid hemorrhage, elderly age and admission hydrocephalus predicted poor outcome, but elderly age without hydrocephalus did not

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Conclusion: In this observational study, elderly age and admission hydrocephalus predicted poor outcome, but elderly age without hydrocephalus did not. An external validation, however, will be needed to generalize this finding.

THE mortality rate of patients with spontaneously ruptured subarachnoid hemorrhage (SAH) is currently more than 30%,[1,2] with most of the mortality occurring during the acute phase in the intensive care unit (ICU).[3] Treatments for SAH during the acute phase include prevention and treatment of early neurologic events such as rebleeding of the aneurysm, hydrocephalus, intracranial hypertension, and ischemic vasospasm.[4,5] It is well established that these major neurologic events are associated with adverse long-term outcomes.[4,6]

The main prognosis scores in the ICU use elderly age as an independent predictor,[7] but the main SAH scores do not.[8,9] Reflecting the aging population worldwide, an increasing proportion of SAH patients are of advanced years,[10] with the definition of elderly SAH patients ranging from 60 yr or older to 70 yr old or older in the literature.[11–15] Although much of the risk prediction research suggests that poor outcome is related not only to age but also to the medical comorbidities associated with age,[16,17] recent studies have shown that elderly age is associated with worse long-term outcomes[18] independently of comorbidities like chronic hypertension.[19] Elderly age also changes the likelihood of the main neurologic complications of SAH, including an increased risk for admission hydrocephalus.[16] Therefore, studies about age-related prognostic markers and outcomes are needed so that medical teams, including anesthesiologists, neurosurgeons, neuroradiologists, and intensivists, can adapt their therapeutic strategies to the needs of elderly SAH patients.

Given that elderly age is associated with poor outcome and that age increases the risk of hydrocephalus, we hypothesized in this study that elderly age would interact with hydrocephalus in outcome prediction. To characterize the effect of hydrocephalus on the impact of age on outcome prediction, we prospectively collected the data of a large cohort of SAH patients during 10 yr and followed each patient's neurologic events in the ICU. To focus on long-term functional outcome, our primary endpoint for this study was 1-yr poor outcome (Rankin 4–6).

Materials and Methods

Patients

From January 1, 2002, to December 31, 2010, we screened 1,000 consecutive adult patients who were admitted to the neurosurgical ICU after a clinical diagnosis of SAH and an aneurysm procedure, and we enrolled 933 patients after they or a family member provided informed consent (fig. 1). The 67 patients not included in the study were admitted to the ICU for diagnosis of SAH but did not receive an aneurysm procedure. All SAH patients at our hospital were admitted to the same neurosurgical ICU. Aneurysm SAH was angiographically confirmed and systematically treated with either a coiling endovascular procedure or clipping surgery. Coiling was performed whenever possible and open surgery was performed when the anatomical structure of the aneurysm increased the risk of the coiling procedure, or when a parenchymatous hematoma was present with significant mass effect at admission. In our prospective cohort, 708 patients

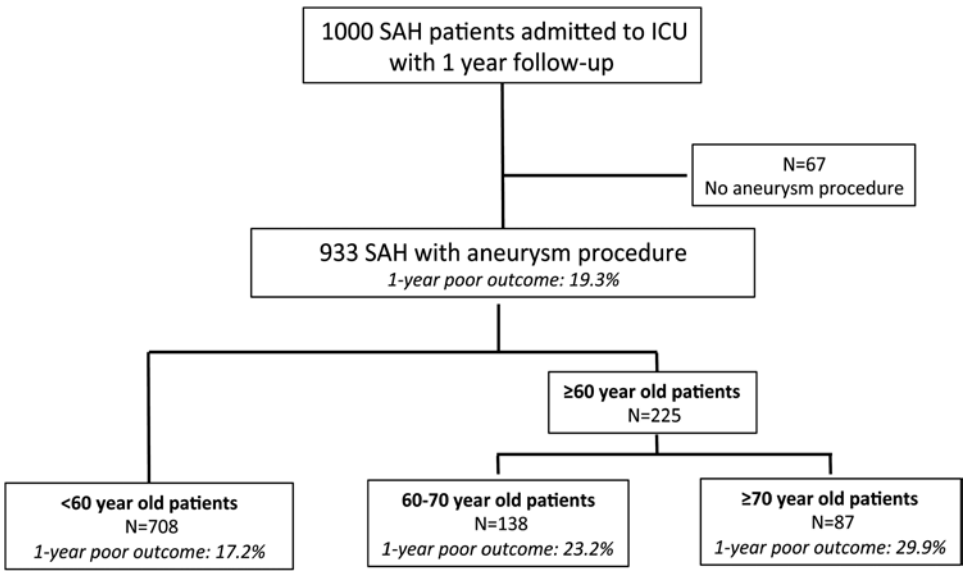

Fig. 1. Flow chart of the 1,000 consecutive subarachnoid hemorrhage patients admitted to the neurosurgical intensive care unit with 1-yr follow-up. We enrolled 933 out of 1,000 consecutive adult patients who were admitted to the neurosurgical intensive care unit after a clinical diagnosis of subarachnoid hemorrhage and an aneurysm procedure. All subarachnoid hemorrhage patients at our hospital were admitted to the same neurosurgical intensive care unit. Rankin scores were obtained from individual patients during systematic 1-yr follow-up visits. Where follow-up visits were impossible, Rankin scores were assessed by a phone call to the patients or their relatives. ICU = intensive care unit; SAH = subarachnoid hemorrhage.

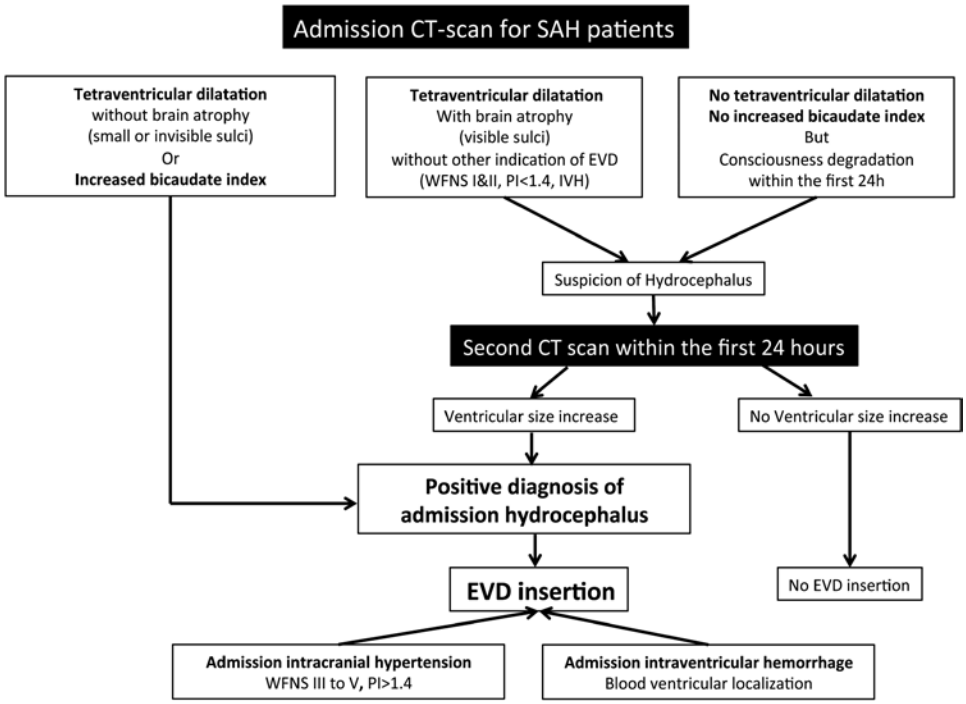

Fig. 2. Algorithm for admission hydrocephalus positive diagnosis and external ventricular drainage. The bicaudate index was calculated as the width of the frontal horns at the level of the caudate nuclei divided by the diameter of the brain at the same level. Increased bicaudate index was defined for each age category as previously established.[23] CT = computed tomography; EVD = external ventricular drainage; IVH = intraventricular hemorrhage; PI = pulsatility index; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgery score.

were younger than 60 yr old and 225 patients were more than 60 yr old, including 87 patients who were more than 70 yr old. The study was approved by the Institutional Review Board of the Assistance Publique – Hôpitaux de Paris, Paris, France, in accordance with the Declaration of Helsinki, and 526 patients in this cohort were included in a previous study[20] registered with ClinicalTrials.gov (NCT01357057). All data were collected and entered by a single coordinator (CC).

Admission Characteristics

We recorded the following admission clinical characteristics: age, sex, Glasgow Coma Scale, presence of clinical seizure, pulmonary edema, and Word Federation of Neurosurgery score (I–V).[8] The Word Federation of Neurosurgery score and Glasgow Coma Scale refer to the Glasgow Coma Scale value at admission, before any treatment with sedative drugs or hydrocephalus treatment.

We also recorded biologic characteristics with routine sampling of S100β protein and cardiac troponin I at admission. S100β concentrations were measured using an immunoluminometric sandwich assay on a LIA-mat 300 analyzer (Byk-Sangtec France Laboratories, Le Mée sur Seine, France) and troponin I was measured with the Troponin Ic assay (Stratus Analyzer, Dade, France). S100β and troponin I levels were considered high for values greater than 0.5 μg/L (corresponding to five times the maximum normal range) to be consistent with previous studies.[20–22]

Concerning radiologic characteristics, the modified Fisher score (I–V)[9] and the presence of hydrocephalus and intraventricular hemorrhage were obtained from the admission computed tomography (CT) scan, according to our institutional algorithm (fig. 2). Briefly, the size of the ventricles and the bicaudate index[23] were used to diagnose hydrocephalus, and the sulci size was used to discriminate between hydrocephalus and brain atrophy. In the case of acute consciousness degradation or large sulci associated with ventricular dilatation, a second CT scan was performed to diagnose hydrocephalus. All admission hydrocephalus cases were treated with an external ventricular drain (EVD). Patients with CT scan evidence of admission hydrocephalus, a Word Federation of Neurosurgery score between III and V, or a transcranial Doppler pulsatility index greater than 1.4 received an EVD before coiling. Admission intracranial hypertension was defined as intracranial pressure greater than 20 mmHg during the EVD procedure. Some patients presented with multiple complications simultaneously (see Supplemental Digital Content 1, http://links.lww.com/ALN/A870, which is a Venn diagram of the external ventricular drainage indications), such as the association of an admission hydrocephalus and increased intracranial pressure (see Supplemental Digital Content 2, http://links.lww.com/ALN/A871, which is an admission hydrocephalus diagnosis according to the increased intracranial pressure status).

In the elderly patient subgroup, comorbidity data were retrospectively extracted from the hospital reports. Of the 225 elderly patients more than 60 yr old, 21 patients had missing or inaccurate comorbidity data. Thus, analyses were performed with the remaining 204 elderly patients (91% of the cohort).

ICU Management and Neurologic Events

All neurologic events during the ICU stay were recorded, including endovascular complications, surgery complications, post-EVD hematoma, admission intraventricular hemorrhage, admission intracranial hypertension, admission hydrocephalus, severe intracranial hypertension, vasospasm, ischemic vasospasm, rebleeding, and EVD infection.

All SAH patients were followed in the ICU using the same therapeutic algorithm to prevent intracranial hypertension.[24,25] EVD infection was controlled according to a preestablished protocol[26,27] (see Supplemental Digital Content 3, http://links.lww.com/ALN/A872, which is the protocol to prevent external ventricular drain-related ventriculitis) that included a single dose of prophylactic antibiotics in the operating room, minimal handling of the catheter, and no rinsing. Coiling and clipping procedures were performed under total IV anesthesia with propofol to prevent movement. Complications that occurred within the first 24 h of the coiling or clipping procedure were recorded. After the procedure, systolic arterial blood pressure was maintained between 130 and 150 mmHg by titrating IV norepinephrine. Severe intracranial hypertension (intracranial pressure greater than 20 mmHg under sedation) was treated by cerebrospinal fluid drainage, deepening of sedation, and, rarely, moderate hypothermia.

We used a previously reported strategy for cerebral vasospasm management.[28] Briefly, all patients received IV nimodipine from admission until the end of the second week after admission. Transcranial Doppler was performed at least once a day during the first 10 days. In the event of clinical deterioration or an increase in mean transcranial Doppler velocities or S100β, a cerebral angiogram was performed after a CT scan ruled out other complications to diagnose the presence of vasospasm. Vasospasm episodes were treated using intra-arterial nimodipine administration, repeated if necessary, and rarely combined with intra-arterial milrinone.[29] Oral statin 1 day after admission to prevent vasospasm injury[30] was introduced in 2006. Ischemic vasospasm was defined as the presence of an ischemic lesion on the control CT scan unrelated to the admission- and procedure-related lesions (*i.e.*, coiling and clipping complications).

Clinical Outcome

The primary endpoint, 1-yr outcome, was systematically assessed using the Rankin outcome scale at 1 yr after ICU discharge.[31,32] Rankin scores were obtained from individual patients during systematic 1-yr follow-up visits. Where follow-up visits were not possible, Rankin scores were assessed by a phone call to the patients or their relatives. The 1-yr Rankin scores were split into good (Rankin 0–3) and poor (Rankin 4–6) functional outcomes. Secondary endpoints, including ICU length of stay, ICU mortality, ICU-free days (with a cutoff at 45 days), ICU Rankin score, 6-month Rankin score, and chronic cerebro-spinal fluid (CSF) shunt insertion were also recorded.

Statistical Analysis

Using the chi-square test for categorical variables and the Student *t* test without Welch correction for continuous variables, we evaluated elderly age (60 yr or more) relative to admission characteristics, neurologic events, and 1-yr outcomes.

We conducted backward and forward stepwise logistic analyses to test associations among all neurologic events, elderly age (adjusted for sex and Fisher score), and 1-yr poor outcome, with a threshold of $P < 0.2$ for inclusion in the model. Once we identified the most parsimonious model for outcome prediction, we analyzed the interaction term that described the relationship between hydrocephalus and elderly age within the multivariate model. Results are reported as odds ratios (OR) with 95% CI. We used a likelihood ratio test to compare models with and without this interaction term. Calibration (Hosmer–Lemeshow goodness-of-fit test) and discrimination (area under the receiver operating characteristic curve, C-statistic) of the models with and without the interaction term between hydrocephalus and elderly age were performed. An internal validation of the model with the interaction term was executed using a jackknife bootstrap resampling method. In the subgroup of elderly patients with complete and accurate medical reports (n = 204), the association between comorbidities and the presence of admission hydrocephalus was quantified with univariate analyses.

Based on similar studies in elderly SAH patients,[16,33,34] the cohort was stratified into three categories (less than 60, 60–70, and 70 yr old or more) to investigate the increasing effect of age on outcome. The significance of age-related trends was tested using the log-odds test. Sensitivity analyses for the seven significant neurologic event subgroups from the most parsimonious model were performed to evaluate the association between stratified age and 1-yr outcome.

Data are expressed as a percentage (with 95% CI) for binary variables, as a median (with 25–75 interquartiles) for discontinuous and nonparametric variables, and as a mean ± SD for continuous variables. All tests are two-sided and all *P* values provided are uncorrected. $P < 0.05$ was considered significant. To take the risk of type-1 error into account in this observational study, we adjusted the *P*-value threshold for each subanalysis with multiple comparisons. Statistical analyses were performed using STATA version 11 (StataCorp, College Station, TX).

Results

The proportion of patients with 1-yr poor outcome was 19.3% (95% CI: 16.8–21.8%), and this proportion was higher in

Table 1. Characteristics of the Overall Population and the Elderly Patients Subgroup

	Overall Cohort (No. = 933)	Elderly Patients 60 Yr Old or Older (No. = 225)	*P* Value
Admission characteristics			
Sex (female)	62.3% (59.2–65.4)	75.6% (43.1–81.2)	<0.001*
Admission GCS	14 (12–15)	14 (12–15)	0.09
Admission WFNS, 3–5	2 (1–4); 55.1% (51.9–58.3)	2 (1–4); 59.1% (52.7–65.6)	0.16
Admission Fisher score, 3–5	3 (2–4); 65.3% (62.2–68.3)	4 (2–4); 72.4% (66.6–78.3)	0.009
Admission Troponin, > 0.5 μg/ml	20.4% (17.8–23.0)	24.0% (18.4–29.6)	0.12
Admission S100β protein, > 0.5 μg/ml	34.1% (31.0–37.1)	36.0% (30.0–42.3)	0.49
Coiling procedure	71.3% (68.4–74.2)	73.8% (68.0–79.7)	0.34
Admission EVD insertion	51.2% (48.0–54.4)	57.8% (51.3–64.3)	0.02
Neurological events			
Admission hydrocephalus	32.6% (29.6–35.6)	44.0% (37.5–50.5)	<0.001*
Admission intracranial hypertension	28.4% (25.5–31.3)	28.4% (22.5–34.4)	0.98
Admission intraventicular hemorrhage	24.9% (21.8–27.6)	28.4% (22.5–34.4)	0.15
Severe intracranial hypertension	9.2% (7.4–11.1)	6.2% (3.0–9.4)	0.07
Vasospasm	30.5% (27.6–33.5)	17.3% (12.3–22.3)	<0.001*
Ischemic vasospasm	9.4% (7.5–11.3)	5.3% (2.4–8.3)	0.02
Rebleeding	1.8% (0.8–2.8)	1.7% (0.4–3.5)	0.96
EVD infection	2.8% (1.7–3.8)	2.2% (0.3–4.2)	0.55
Endovascular complication	13.2% (11.0–15.4)	16.4% (11.6–21.3)	0.09
Surgery complication	12.2% (10.1–14.3)	11.6% (7.3– 15.8)	0.72
Post-EVD hematoma	1.8% (0.1–2.7)	1.3% (0–2.8)	0.53
Outcomes			
Chronic CSF shunting	8.6% (6.8–10.4)	12.4% (8.1–16.8)	0.02
LOS ICU (days)	22 ± 24	27 ± 24	<0.001*
ICU mortality	16.9% (14.5–19.3)	19.6% (14.3–24.8)	0.23
ICU free days (45 days)	20 ± 20	16 ± 16	<0.001*
Rankin ICU release	2 (1–3)	2 (1–4)	<0.001*
1-yr Rankin	1 (0–2)	1 (0–4)	<0.001*
1-yr mortality	18.5% (16.0–21.0)	23.6% (18.0–29.1)	0.03
1-yr poor outcome	19.3% (16.8–21.8)	25.8% (20.0–31.5)	0.005

Values are expressed as a mean ± SD, median with interquartile (25–75), or percentage with 95% CI. 1-yr poor outcome was defined as a Rankin score between 4 and 6. Elderly patients were defined as 60 yr old or more. Mean ages of the overall cohort and the elderly patients were 50 ± 13 and 68 ± 6 yr old, respectively. *P* values refer to comparisons between the 60-yr-old or more (elderly) group and the 60-year-old and younger group.

* $P < 0.0019$ corresponding to significant *P* values below the adjusted significance level for multiple comparisons.

CSF = cerebrospinal fluid; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICU = intensive care unit; LOS = length of stay; WFNS = World Federation of Neurological Surgeons.

patients 60 yr old or more than in patients less than 60 yr old (fig. 1). Across the 10 years in which the study was conducted, the proportions of patients with 1-yr mortality and 1-yr poor outcome were similar ($P = 0.73$ and $P = 0.56$, respectively). Regarding admission characteristics, the 60-yr-old or more subgroup presented a significantly higher proportion of both female patients and patients with high Fisher scores ($P < 0.001$ and $P = 0.009$, respectively, table 1). We did not observe statistical differences for any other admission characteristics. Regarding neurologic events, the elderly subgroup did not experience more neurologic events overall than patients less than 60 yr old ($P = 0.11$). The 60-yr-old or more subgroup did present with admission hydrocephalus more often ($P < 0.001$) and with vasospasm less often ($P < 0.001$); other neurologic events did not statistically differ between the age subgroups. Except for ICU mortality, the elderly patient subgroup was statistically more likely to present short- and long-term poor outcomes (table 1).

Elderly Age and 1-yr Poor Outcome Associations through Hydrocephalus

Forward and backward stepwise analyses both defined the same variables to compose the most parsimonious model. In this model, admission hydrocephalus, admission intracranial hypertension, severe intracranial hypertension, ischemic vasospasm, rebleeding, endovascular and surgery complications, elderly age, and high Fisher score were all independently associated with 1-yr poor outcome ($P < 0.05$ for each event, table 2), whereas sex, admission intraventricular hemorrhage, EVD hematoma, and EVD infection were not. Concerning elderly age, the OR for 1-yr poor outcome prediction was 2.08 (95% CI: 1.34–3.21, $P < 0.001$). Then we tested the interaction between admission hydrocephalus and elderly age, which we found to be significant ($P = 0.04$). The likelihood ratio test comparing the model with and without the interaction term

Table 2. Stepwise Logistic Regressions of the Association between Neurological Events, Elderly Age, and 1-yr Poor Outcome

	Overall Multivariable Analyses		Stepwise Multivariable Analyses (for Variables with $P < 0.2$)			
	Odds Ratio (95% CI)	*P* Value	*P* Value	*P* Value	*P* Value	*P* Value
Vasospasm	0.89 (0.54–1.49)	0.66	—	—	—	—
Post-EVD hematoma	1.17 (0.33–4.22)	0.81	—	—	—	—
Admission intraventricular hemorrhage	1.47 (0.87–2.48)	0.15	0.16	—	—	—
Female	0.71 (0.47–1.07)	0.10	0.1	0.09	—	—
EVD infection	0.24 (0.05–1.24)	0.09	0.09	0.09	0.09	—
Admission hydrocephalus	1.71 (1.10–2.68)	0.02	0.02	0.002	0.002	0.004
Rebleeding	6.11 (1.64–22.7)	0.007	0.007	0.005	0.006	0.005
High Fisher score (III–V)	2.46 (1.37–4.42)	0.001	0.003	0.001	0.001	0.001
Elderly age (60 yr old or older)	2.22 (1.40–3.50)	0.001	0.001	<0.001	0.001	0.001
Admission intracranial hypertension	3.00 (1.88–4.80)	<0.001	<0.001	<0.001	<0.001	<0.001
Severe intracranial hypertension	3.73 (2.15–6.47)	<0.001	<0.001	<0.001	<0.001	<0.001
Ischemic vasospasm	4.90 (2.55–9.43)	<0.001	<0.001	<0.001	<0.001	<0.001
Endovascular complication	2.78 (1.66–4.64)	<0.001	<0.001	<0.001	<0.001	<0.001
Surgery complication	4.48 (2.58–7.64)	<0.001	<0.001	<0.001	<0.001	<0.001

Backward stepwise logistic regressions included all the neurological events and elderly age (adjusted for sex and high Fisher score). Forward stepwise analyses showed that the same nine variables were independently associated with 1-yr poor outcome (not shown).
EVD = external ventricular drain.

for age and admission hydrocephalus showed a significant improvement with the interaction ($P = 0.03$). However, when the interaction with hydrocephalus was included in the model, elderly age and admission hydrocephalus were no longer predictors on their own ($P = 0.48$ and $P = 0.20$, respectively, table 3).

Increased Age Effects and 1-yr Poor Outcome Association

To understand if the association between age and 1-yr poor outcome increased with age, we stratified age into three categories. In this cohort, 24.1% of patients were more than 60 yr old, including 14.8% of patients who were 60–70 yr old, and 9.3% of patients who were more than 70 yr old,

Table 3. The Most Parsimonious Model for Predicting 1-yr Poor Outcome with and without the Age–Hydrocephalus Interaction

	Parsimonious Model without Interaction		Parsimonious Model with Age–Hydrocephalus interaction	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Admission intracranial hypertension	3.62 (2.40–5.46)	<0.001	3.58 (2.37–5.41)	<0.001
Severe intracranial hypertension	3.51 (2.04–6.02)	<0.001	3.54 (2.06–6.08)	<0.001
Ischemic vasospasm	4.34 (2.49–7.59)	<0.001	4.67 (2.51–7.66)	<0.001
Rebleeding	6.75 (1.80–25.3)	0.005	6.31 (1.69–23.6)	<0.001
Endovascular complication	2.91 (1.75–4.84)	<0.001	3.10 (1.85–5.19)	<0.001
Surgery complication	4.25 (2.51–7.20)	<0.001	4.44 (2.61–5.19)	<0.001
High Fisher score (III–V)	2.65 (1.48–4.77)	0.001	4.44 (1.52–4.88)	<0.001
Admission hydrocephalus	1.83 (1.21–2.77)	0.004	1.38 (0.84–2.26)	0.20
Elderly age (60 yr old or older)	2.08 (1.34–3.21)	0.001	1.26 (0.66–2.43)	0.48
Interaction term for admission hydrocephalus and elderly age	—	—	2.56 (1.06–6.17)	0.04

P values for the goodness-of fit test (Hosmer–Lemeshow) for the models with and without age-interaction were 0.22 and 0.18, respectively. Calibrations (area under the receiver operating characteristic curve, C-statistics) for the models with and without age-interaction were 0.85 (95% CI: 0.82 to 0.88; $P < 0.001$) and 0.84 (95% CI: 0.82 to 0.88; $P < 0.001$), respectively. Likelihood ratio test comparing the models with and without elderly age interaction term showed a significant improvement with the inclusion of the interaction term ($P = 0.03$). Internal validation of the model (jackknife bootstrap resampling with 1,000 replicates) showed that the odds ratio of the interaction term for age and admission hydrocephalus was 2.57 (95% CI: 1.01–6.53, $P = 0.04$) with similar *P* values for the other variables in the model.

Table 4. Age-related Trends for Admission Characteristics, Neurological Events, and Outcomes

	Odds Ratio for 60–70-yr-old Patients (95% CI)	Odds Ratio for 70-yr-old or Older Patients (95% CI)	*P* Value (Trend Odds)
Admission characteristics			
Female	1.90 (1.27–2.85)	2.98 (1.70–5.19)	<0.001*
WFNS 3–5	1.16 (0.77–1.62)	1.47 (0.93–2.40)	0.10
Fisher 3–5	1.60 (1.06–2.41)	1.46 (0.89–2.37)	0.02
Seizure	0.81 (0.50–1.33)	0.57 (0.28–1.11)	0.07
Pulmonary edema	2.56 (1.17–5.57)	0.78 (0.18–3.34)	0.41
Troponin > 0.5 μg/mL	1.32 (0.85–2.04)	1.34 (0.79–2.26)	0.15
S100β protein > 0.5 μg/mL	0.96 (0.65–1.42)	1.40 (0.89–2.21)	0.25
Clipping procedure	0.84 (0.56–1.27)	0.85 (0.51–1.42)	0.39
EVD	1.47 (1.01–2.13)	1.33 (0.85–2.09)	0.05
Neurological events			
Admission intracranial hypertension	1.18 (0.80–1.75)	0.75 (0.44–1.27)	0.60
Admission hydrocephalus	1.73 (1.18–2.52)	2.29 (1.45–3.61)	<0.001*
Admission intraventricular hemorrhage	1.36 (0.90–2.04)	1.15 (0.79–1.92)	0.27
Severe intracranial hypertension	0.84 (0.44–1.60)	0.20 (0.05–0.87)	0.02
Vasospasm	0.40 (0.25–0.63)	0.39 (0.22–0.70)	<0.001*
Ischemic vasospasm	0.51 (0.24–1.09)	0.40 (0.14–1.13)	0.02
Surgery complication	0.78 (0.37–1.62)	1.79 (0.75–4.28)	0.41
Endovascular complication	1.68 (1.03–2.72)	1.05 (0.53–2.05)	0.30
Rebleeding	0.39 (0.05–3.01)	1.90 (0.53–6.85)	0.61
EVD infection	0.73 (0.21–2.47)	0.77 (0.18–3.34)	0.60
Post EVD hematoma	0.73 (0.16–3.24)	0.58 (0.07–4.45)	0.52
Outcomes			
Chronic CSF shunting	2.34 (1.33–4.13)	1.53 (0.70–3.40)	0.03
ICU mortality	1.04 (0.64–1.70)	1.66 (0.97–2.82)	0.10
1-year mortality	1.36 (0.87–2.14)	1.76 (1.05–2.95)	0.02
1-year poor outcome	1.45 (0.98–2.56)	2.05 (1.24–3.38)	0.002*

P values refer to tests of the trend of odds for each criterion. 1-yr poor outcome was defined as a Rankin score between 4 and 6.
* $P < 0.0022$ corresponding to significant *P* values below the adjusted significance level for multiple comparison with 23 variables.
CSF = cerebrospinal fluid; EVD = external ventricular drain; ICU = intensive care unit; WFNS = World Federation of Neurological Surgeons.

and these proportions were similar across the study period ($P = 0.08$, $P = 0.21$, and $P = 0.69$, respectively). Stratified age showed a trend of an increasing proportion of female patients ($P < 0.001$, table 4). Interestingly, stratified age did not significantly differ for other patient characteristics (table 4). Stratified age increased the odds of 1-yr poor outcome ($P = 0.002$, fig. 3A). Concerning neurologic events, only hydrocephalus at admission (fig. 3B) tended to increase with stratified age ($P < 0.001$, table 4), whereas vasospasm (fig. 3B) showed a statistically decreasing trend ($P < 0.001$). The age-related impact of hydrocephalus was also observed in the 1-yr survival curve in the overall population and in the subgroup with hydrocephalus, but not in the subgroup without hydrocephalus (see Supplemental Digital Content 4, http://links.lww.com/ALN/A873, which is the 1-year survival curve according to stratified age). We did not find any significant association between admission hydrocephalus and the major comorbidities in the elderly subgroup (table 5).

The sensitivity analyses of the association between stratified age and 1-yr poor outcome was performed for the seven significant neurologic events defined by the most parsimonious model. We found that the association between stratified age and 1-yr poor outcome was significant in the overall population ($P = 0.002$) and the hydrocephalus subgroup ($P = 0.007$), but not in the subgroup without hydrocephalus ($P = 0.86$) or any other subgroup (table 6, fig. 3C).

Discussion

In this observational study that enrolled 933 consecutive SAH patients who were followed for 1 yr after discharge from the same ICU, we found that elderly age and admission hydrocephalus were both associated with 1-yr poor outcome, and that elderly age was associated with 1-yr poor outcome only in the presence of admission hydrocephalus. Furthermore, the association between admission hydrocephalus and 1-yr poor outcome increased with age.

Elderly Patients and Outcome Prediction

The average age of patients in the ICU, and especially the neuro-ICU,[33,35] is rising. Unfortunately, studies designed to test the safety and efficacy of the primary aneurysmal SAH treatments have not been controlled for differential outcomes in elderly patients,[36] who are more likely to have additional medical conditions that negatively impact outcomes for a wide range of diseases and their treatments. Elderly SAH patients may not be able to tolerate the primary injuries and aggressive treatments as well as younger patients. Most likely

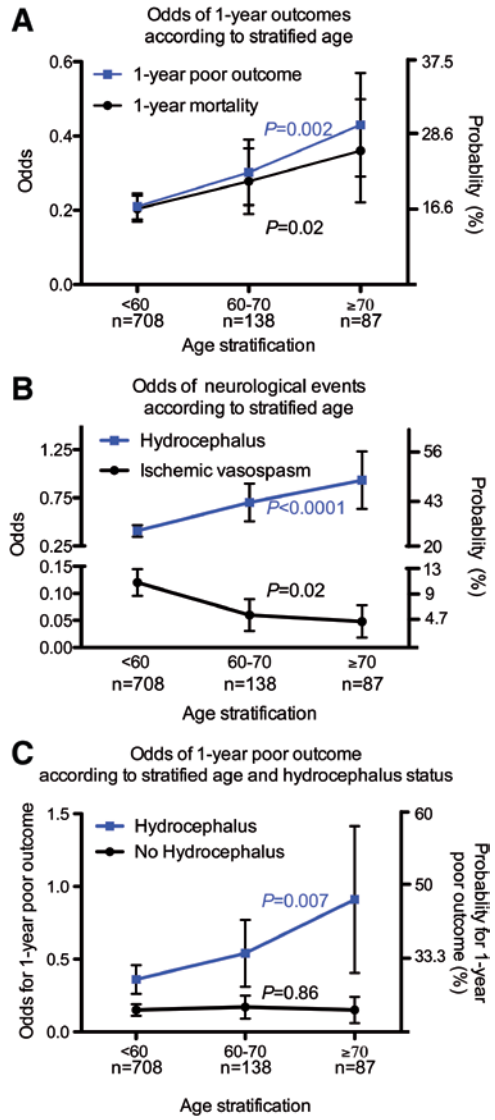

Fig. 3. Odds ratio values according to age for (*A*) 1-yr outcomes, (*B*) neurologic events, and (*C*) the association between neurologic events and 1-yr poor outcome. *Dots* represent mean odds ratio with the 95% CI for each age group. (*A*) The *P* values for the increasing trend of odds were 0.002 for 1-yr poor outcome and 0.02 for 1-yr mortality. (*B*) The *P* values for the increasing trend of odds were less than 0.001 for hydrocephalus and 0.02 for the decreasing trend of odds for ischemic vasospasm. (*C*) The *P* values for the trend of odds were 0.86 for patients without hydrocephalus and 0.007 for patients with hydrocephalus.

because of age-related deterioration of organ and body system function, elderly age has independently been associated with poor SAH outcomes in previous studies.[17] Because the elderly population is a heterogeneous one,[37,38] and because age-related deterioration is not easy to quantify in the process of ICU admission, clinicians need better tools to characterize patient subgroups to predict long-term outcomes.

However, age correlates with both comorbidities and some neurologic complications, and it is not clear which of these pathways is most relevant to the impact of age on outcome prediction. Previous studies have mainly focused on the potential effects of comorbidities, but Rosengart *et al.* found that age, but not history of hypertension, was a significant predictor for poor outcome at 3 months in a Cox proportional hazards regression.[19] One reason could be that a history of a comorbidity like hypertension may depend on whether the patient was previously diagnosed and is currently receiving treatment.

Even if there were no causal link between age and outcome, age is generally used as a predictor for poor outcome in the ICU,[7] most likely because age is not subject to measurement bias and because it can aggregate the effects of several other conditions. In other words, even though age can be an independent predictor, it is most likely not causally related to poor outcome, but instead mediated by other factors, *i.e.*, comorbidities and neurologic complications. However, for this study we chose to focus not on comorbidity data, which can be unreliable because of interindividual variability in diagnosis-seeking behavior and treatment adherence, but on data that can be easily assessed in the ICU, specifically age and neurologic events, especially hydrocephalus.

Specific Phenotype of Elderly Patients

In our cohort, elderly age was associated with female sex, higher Fisher scores, hydrocephalus at admission, and most importantly, poor long-term outcome. Interestingly, our data confirmed the highly debated observation that elderly patients are less likely than patients less than 60 yr old to experience vasospasm.[11,39,40]

The reported incidence of hydrocephalus in elderly patients varies widely, ranging from 4% to 55%.[41,42] This range may arise from different definitions and diagnostic methods for hydrocephalus in different studies. In our study we used the admission CT scan to diagnose hydrocephalus (fig. 2), and a second CT scan was performed before the EVD insertion if the diagnosis was controversial. One difficulty with diagnosing hydrocephalus is discriminating between hydrocephalus and brain atrophy,[23] and brain atrophy is more common in elderly patients.[43] In our algorithm for diagnosing hydrocephalus, we took into account the sulci sizes to distinguish brain atrophy from acute hydrocephalus. Even though we avoided unnecessary EVD insertions by assessing the sulci sizes, it is important to note that brain atrophy is always a potential measurement bias for the diagnosis of admission hydrocephalus. Because all patients with a positive diagnosis of admission hydrocephalus were treated, we were not able to evaluate the potential negative impact of untreated hydrocephalus in elderly patients.

The higher incidence of hydrocephalus in elderly patients may be related to a number of factors.[44,45] First, in the context of SAH, the accumulation of blood within the subarachnoid space temporarily degrades CSF reabsorption.[42] Because CSF reabsorption function decreases with age,[44] elderly patients may be particularly susceptible to CSF reabsorption dysfunction

Table 5. Association between Admission Hydrocephalus and Comorbidities in the Elderly Group

Comorbidities	No. of Patients with the Comorbidity (%)	Odds Ratio for the Association with Admission Hydrocephalus (95% CI)	*P* Value
Treatment for hypertension	99 (48.5%)	0.80 (0.46–1.40)	0.44
Treatment for dyslipidemia	59 (28.9%)	0.75 (0.40–1.40)	0.37
History of smoking	46 (22.6%)	1.20 (0.62–2.33)	0.59
Morbid obesity	20 (9.8%)	0.56 (0.21–1.51)	0.25
Treatment for diabetes	17 (8.3%)	1.24 (0.46–3.40)	0.67
Treatment for arrhythmia	11 (5.4%)	1.05 (0.50–5.74)	0.40
Atherosclerosis disease	20 (9.8%)	0.91 (0.35–2.32)	0.84
Brain disease	15 (7.4%)	0.67 (0.22–2.03)	0.48

Comorbidities data of the elderly patients were extracted retrospectively from the hospital reports. Out of the 225 patients, 21 patients were presenting missing or inaccurate data. Univariate analyses for the association with admission hydrocephalus were performed with the 204 remaining elderly patients (91% of the cohort), including 86 patients with admission hydrocephalus (42.2%). Morbid obesity is defined as an admission body mass index of more than 30 kg/m^2. Antecedent of atherosclerosis disease includes carotid, coronary, and peripheral arterial stenosis disease. Antecedent of brain disease includes ischemic stroke, subarachnoid hemorrhage, and traumatic brain injuries.

after SAH. However, we were not able to find any association between major comorbidities and the hydrocephalus status at admission in our subgroup of elderly patients. Second, because the degree of hemorrhage (*i.e.*, the Fisher score) is known to be associated with hydrocephalus[46] and, in our study, with elderly age, the higher incidence of hydrocephalus in elderly patients may be linked with increased subarachnoid bleeding in elderly patients. Therefore, to address whether hydrocephalus can independently predict long-term outcome, we adjusted for the Fisher score. However, the Fisher score is not a quantitative estimation of SAH bleeding, and once quantitative measurements are validated in future studies, they may be more sensitive than the Fisher score.

Table 6. Sensitivity Analyses of the Association between Stratified Age and 1-yr Poor Outcome According to Neurological Events

	No. of Patients	Odds Ratio (95% CI)	*P* Value
Admission hydrocephalus	304	1.56 (1.13–2.15)	0.007*
Admission intracranial hypertension	265	1.36 (0.92–2.04)	0.13
Severe intracranial hypertension	86	1.24 (0.46–3.32)	0.67
Vasospasm	285	1.48 (0.91–2.40)	0.11
Ischemic vasospasm	88	1.07 (0.45–2.52)	0.87
Endovascular complication	123	0.71 (0.38–1.31)	0.27
Surgery complication	114	1.62 (0.93–2.82)	0.08

Only neurological events presented in the most parsimonious model were included in the sensitivity analyses. The association between stratified-age in the overall population was significant (OR: 1.43; 1.14 to 1.81, $P = 0.002$), whereas it was not significant in patients without hydrocephalus at admission (n = 629, OR: 1.04; 0.70 to 1.52, $P = 0.86$).

* $P < 0.0071$ corresponding to significant *P* values below the adjusted significance level for multiple comparison.

OR = odds ratio.

Admission Hydrocephalus as a Risk Factor for Elderly Patients

Our study showed that hydrocephalus was a strong and independent admission prognostic marker of 1-yr poor outcome, especially in elderly patients, with the risk of 1-yr poor outcome increasing with age. In our cohort, all hydrocephalus patients were rapidly treated with EVD. Elderly patients who experienced acute CSF reabsorption dysfunction were more likely to have poor long-term outcomes. Even if we had not been able to explore the causal link between admission hydrocephalus and long-term outcome, sensitivity analyses showed that this age-related association disappeared in the subgroup of patients without hydrocephalus. To interpret this finding, hydrocephalus could be related to the patient's lack of CSF reabsorption reserves, irrespective of the amount of blood in the subarachnoid space. In this case, hydrocephalus would in fact be a prognostic marker of general biologic age in addition to long-term outcome.

It is also important to note that age did not influence long-term outcomes in patients without hydrocephalus at admission. In other words, patients without hydrocephalus had a similar likelihood of a poor outcome, whether they were less than 60 or more than 70 years of age.

Study Limitations

This study demonstrated an interaction between age and hydrocephalus but did not infer any causal link among admission hydrocephalus, elderly age, and 1-yr poor outcome.

The first limitation of this study is that it was performed at only one center, because survival and long-term outcomes may be dependent on ICU management and the population studied. However, the advantage of our study was that all patients were managed in highly standardized conditions that allowed us to identify clinically relevant independent prognostic factors.[24,27,28] To reduce interobserver variability in diagnostic and therapeutic strategies and database coding, institutional algorithms were used to diagnose and treat patients, and a single physician coded the database. Even though we took into

account the importance of the type-1 risk in a cohort study like ours by adjusting for multiple comparisons in our analyses, we acknowledge that this study was observational without any external validation. Therefore, a prospective and multicenter study featuring different ICU therapeutic strategies should be conducted to confirm the value of admission hydrocephalus as an age-specific risk factor of long-term outcome after SAH.

Because the aneurysm treatment could potentially influence the incidence of neurologic events,[47] we ensured that the neurologic events, especially hydrocephalus, were still associated with 1-yr poor outcome after adjusting for the clipping and coiling procedures (data not shown). However, the size of the cohort did not allow us to perform multivariate analysis in the clipping and coiling subgroups. Comparing the association between admission hydrocephalus and long-term outcome in the clipping and coiling subgroups would be highly interesting in this context.

Because we did not lose any patients on systematic 1-yr follow-up visits or phone calls, and because we chose the 1-yr outcome as the primary endpoint, we decided to build our models using logistic regression instead of time-varying parameter Cox models. In our logistic regression models, we adjusted for mediators (*i.e.*, Fisher score and sex) to exclude potential confounders. Adjustments gave us the opportunity to show an independent interaction between elderly age and hydrocephalus, but they may have underestimated the age-related interactions of this neurologic event.

In this study, we found that the incidence of 1-yr poor outcome increased dramatically in patients more than 60 yr old, as corroborated in the SAH literature,[16,48] and that age interacted with admission hydrocephalus in outcome prediction. Our age stratification allowed us to show an increasing trend of odds of 1-yr poor outcome with hydrocephalus and with increasing age. However, because this study was conducted at one center and one country only, it is necessary to point out that cultural factors in different countries could affect treatment strategies and outcomes.[49]

Conclusions

This is the first observational study to provide large cohort-based evidence that elderly age is associated with admission hydrocephalus and 1-yr poor outcome, and that elderly age is a prognostic marker for long-term outcome through its interaction with admission hydrocephalus. These results show an age-dependent impact of an early neurologic event on long-term outcome prediction. However, external validation studies are needed to confirm these results.

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