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ORIGINAL ARTICLE

Prediction of evolution toward brain death upon admission to ICU in comatose patients with spontaneous intracerebral hemorrhage using simple signs

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Summary

The aim of the study was to identify the predictors of brain death (BD) upon admission to the intensive care unit (ICU) of comatose patients with spontaneous intracerebral hemorrhage (ICH). Patients admitted in our ICU from 2002 to 2010 for spontaneous ICH and placed under mechanical ventilation were retrospectively analyzed. Of the 72 patients, 49% evolved to BD, 39% died after withdrawal of life support, and 12% were discharged alive. The most discriminating characteristics to predict BD were included in two models; Model 1 contained ≥ 3 abolished brainstem responses [adjusted odds ratios (OR) = 8.4 (2.4, 29.1)] and the swirl sign on the baseline CT-scan [adjusted OR = 5.0 (1.6, 15.9)] and Model 2 addressed the abolition of corneal reflexes [unilateral/bilateral: adjusted OR = 4.2 (0.9, 20.1)/8.8 (2.4, 32.3)] and the swirl sign on the baseline CT-scan [adjusted OR = 6.2 (1.9, 20.0)]. Two scores predicting BD were created (sensitivity: 0.89 and 0.88, specificity: 0.68 and 0.65). Risk of evolution toward BD was classified as low (corneal reflexes present and no swirl sign), high (≥ 1 corneal reflexes abolished and swirl sign), and intermediate. Simple signs at ICU admission can predict BD in comatose patients with ICH and could increase the potential for organ donation.

Introduction

Early prediction of evolution toward brain death (BD) in comatose patients with stroke is of great interest as BD is currently in France the primary source of organ donation (80%) [1,2]. Recently, the recommendations of French societies regarding stroke management outlined that comatose patients with stroke and very bad prognosis could ethically be admitted to ICU if evolution toward BD, allowing a potential organ donation, seems likely [3]. However, to date, no accurate criteria predicting evolution toward BD in comatose patients with stroke has been reported.

Spontaneous intracerebral hemorrhage (ICH) is the deadliest type of stroke and is a leading cause of mortality and morbidity worldwide [4–7]. The two main causes of death after ICH admitted to ICU are withdrawal of life support for perceived futility of care and BD [8–10]. Although many studies have evaluated early predictors of neurological outcomes after ICH, none specifically sought to identify predictors of BD. Most of these studies pooled the nonsurvivors, without specifically identifying brain-dead patients [6,11–16].

To better identify potential organ donors, some experts have recently proposed definitions of "imminent BD" [17,18]. In a retrospective cohort of patients who died from ICH, aneurysmal subarachnoid hemorrhage, or traumatic brain injury, a third of patients who fulfilled the criteria for "imminent BD" were ultimately organ donors after BD [18]. However, other patients who died as result of BD, but did not become organ donors were not reported. Recently, analyzing patients who died in ICU in Dutch university hospitals, it has been reported that 45.6% of patients with "imminent BD" actually evolved toward BD [19]. However, "imminent BD" definitions were not evaluated upon admission to the ICU.

The aim of the current study was to identify, upon ICU admission, early predictors of evolution toward BD in comatose patients with ICH.

Patients and methods

The database used for this study received the required legal approval from the appropriate French data protection committee (Commission Nationale de l'Informatique et des Libertés). This study was approved by the Ethics Committee of the Société de Réanimation de Langue Française. In accordance with the French regulation on investigations of information contained in databases, the requirement for written informed consent was waived and was replaced by information provided to patients when possible or their next of kin.

We conducted a retrospective study in our 14-bed medical ICU from 2002 to 2010. There is no neurosurgical unit or neurological ICU in our tertiary teaching hospital. Patients are admitted to our ICU only in the absence of a neurosurgery requirement. According to the usual management of these patients in the Paris area, patients initially managed at home by medical mobile emergency units are admitted to our ICU only after having first been conducted to a neurosurgical unit to be explored by computed tomography (CT) and examined by a neurosurgeon. Similarly, CT scans of patients from the emergency ward of our hospital are always transferred by computer network to a neurosurgical unit, and the opinion of a neurosurgeon is always required.

We decided to analyze the data on comatose patients admitted to the ICU for spontaneous ICH and placed under mechanical ventilation. Data were extracted for "ICH" and "mechanical ventilation" to identify patients from computerized ICU discharge reports. Charts were reviewed to identify coding mistakes. To homogenize the study population, we excluded patients with ICH related to trauma, hemorrhagic transformation after acute ischemic stroke, isolated subarachnoid hemorrhage, patients who required neurosurgery, patients transferred from another ward after BD diagnosis, patients in BD upon the admission, patients whose death was nonneurological (cardiac arrest, septic shock, or other medical cause), and patients with missing data.

Medical reports and charts were manually reviewed to collect clinical data. Neurological examinations upon ICU admission were collated. The level of consciousness was assessed using the motor and eye responses of the Glasgow Coma Scale [20]. As patients could have been placed under mechanical ventilation by the medical mobile emergency unit before ICU admission, we also collected assessments of the Glasgow Coma Scale performed just before placement under mechanical ventilation. Data from assessments of pupil size (miosis, normal, or mydriasis) and five brainstem reflexes were collected in the charts: response to light, corneal reflexes, oculocephalic response to lateral passive head rotation, cough response after tracheal suctioning, and spontaneous ventilation. Spontaneous ventilation was assessed during an apnea test after disconnection between the tracheal tube and the ventilator to avoid cardiogenic ventilator autotriggering [21]. The number of abolished brainstem responses at admission was calculated; pupillary response to light and corneal reflexes were considered abolished if they were bilaterally absent. Other clinical characteristics evaluated at admission, such as temperature, arterial pressure, and heart rate, and biological results were also collected. Coagulation disorder was defined as platelet levels <100 G/l or International Normalized Ratio ≥ 1.5 or activated partial-thromboplastin time ratio ≥ 1.26 or treatment by platelet aggregation inhibitor. The Simplified Acute Physiology Score II [22] was calculated after 24 h.

Baseline CT scans were independently analyzed by a neuroradiologist and a neurologist who were blinded to patient clinical data and outcome. Joint decisions were made by both reviewers in cases of disagreement. Data collected were: time from onset to CT, location of ICH, volume of ICH, peri-ICH edema, the swirl sign, associated intraventricular hemorrhage, and brain herniation (subfacial, uncal, or cerebellar tonsillar). The ICH volume was calculated according to the established ABC/2 technique [23,24], and the amount of intraventricular hemorrhage was characterized using the Intraventricular Hemorrhage Score [25,26]. The swirl sign can be seen on unenhanced CT scans and it represents active bleeding in the hematoma. It represents actively extravasating unclotted fresh blood which is of lower attenuation than clotted blood (typically 50–70 HU) which surrounds it [27–30]. The clinico-radiological ICH score was calculated by assessing the Glasgow Coma Scale just before placement under mechanical ventilation [31,32].

In accordance with French law, BD was assessed by two independent physicians and required fulfillment of all the following criteria: (i) absence of consciousness (areactive comatose state) that cannot be explained by hypothermia or treatment, (ii) abolition of all brainstem reflexes including an apnea test performed until $PaCO_2$ rose from 35–40 mmHg to >60 mmHg to ensure loss of intrinsic respiratory drive and carbon dioxide reactivity, and (iii) confirmatory test demonstrating the loss of bioelectrical activity by two isoelectric electroencephalograms recorded for at least 30 min 4 h apart, or absence of brain circulation as assessed by enhanced CT scan or arteriography [33]. As patients could remain in the ICU for several days after BD diagnosis for organ donation organization, the length of ICU stay was calculated from admission to BD diagnosis.

Clinical evaluation of patients was performed every 4 h by the full-time intensivist medical team. Patients with ICH admitted to our ICU were managed according to our local protocol adapted from established guidelines [3,34].

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges, and categorical variables were expressed as numbers and percentages. Variables were compared using Fisher's exact test or Wilcoxon test as appropriate. We considered *P* value <0.05 as significant. Our primary objective was to find a simple predictive rule for BD. It is well known that the performance of such a rule, when it is formulated and assessed on the same data set, will tend to be overestimated. To correct for this over-optimism, data mining techniques like classification trees favor the construction of predictive rules of minimal complexity [35]. Classification trees use iterative hierarchical partitioning of the sample according to the most discriminating variables. At each step, a simple rule for splitting the sample is retained that leads to the largest decrease in the Gini index, a measure of heterogeneity [35]. The number of rules retained to split the sample was determined by cross-validation. A useful extension to classification trees is the so-called "random forest": This is a collection of classification trees built as above, each one obtained from a random subset of observations from the original sample [35]. By inspecting what variables were retained in each of the trees, it is possible to measure the importance of candidate predictors, by computing the loss of prediction accuracy when it is randomly permuted in the sample. To summarize the results, we finally fitted a logistic regression model using the variables identified in the classification trees. Inter-rater agreement for CT scan interpretation was assessed by the Cohen's kappa coefficient. Scores were compared using the Youden index or AUROC.

Results

Of the 90 patients identified from computerized ICU discharge reports, 18 were not included in the analysis according to exclusion criteria (six were transferred for or after neurosurgery, four had hemorrhagic transformation after ischemic stroke, seven for missing data and 1 had MRI without CT scan). Of the 72 patients analyzed, 35 (49%) evolved toward BD, 28 (39%) died in the ICU after withdrawal of life support, and 9 (12%) were discharged alive from the ICU. Of the 35 patients who evolved toward BD, organ donation was performed in 16 cases (46%), refused by close relatives in nine cases (26%), and contraindicated by medical history or acute organ failure in 10 cases (28%). The length of stay in the ICU was shorter for patients who died from BD than for other patients [2 (2–3) vs. 7 (5–11) days, $P < 0.0001$]. Only one patient evolved to BD after the third day. Among patients who did not die from BD, the length of stay in the ICU was longer for patients who survived to ICU [17 (6–26) days] than for patients who died after withdrawal of life support [7 (5–9) days; $P < 0.04$]. Of the nine patients who were discharged alive from the ICU, three died in the hospital. At hospital discharge, three patients had a modified Rankin Scale score [36–38] of 5 (severe disability), one patient had a score of 3 (moderate disability), and two patients had a score of 1 (no significant disability).

Characteristics at ICU admission were compared according to the patient outcome at ICU discharge (Table 1). Characteristics exhibiting significant differences between groups were the neurological examination at admission, the swirl sign, and presence of cerebellar tonsillar herniation on the first CT scan. Biological characteristics were similar between groups (Table 1).

Predictors for evolution toward BD were identified by classification trees. The best predictors for evolution toward BD were ≥ 3 abolished brainstem responses upon admission to the ICU and the swirl sign on the first CT scan. The evolution toward BD happened in 31/43 (72%) patients with at least one of these 2 characteristics and in 4/29 (13%) patients with none of these characteristics. The random forest analysis showed that, in addition to the two variables listed above, abolition of corneal reflexes was also a good predictor of BD (Fig. 1). These data mining techniques allowed to identify the three most discriminating variables to predict evolution toward BD. We further investigated the characteristics of the prediction rule with two models.

Model 1 included ≥ 3 abolished brainstem responses upon admission to the ICU and the swirl sign on the first CT scan, while Model 2 included the abolition of corneal reflexes upon admission to the ICU and the swirl sign on the first CT scan (Table 2). Both models confirmed the strong association of identified variables with evolution toward BD. The score for Model 1 was calculated by attributing one point per variable (≥ 3 abolished brainstem responses and the swirl sign). The score for Model 2 was

Table 1. Characteristics of patients upon admission to the intensive care unit.

Variables	Evolution toward brain death Yes (n = 35)	No (n = 37)	P-value
Clinical characteristics			
Gender, male, n (%)	17 (49)	24 (65)	0.24
Age, years	73 (61–81)	70 (64–78)	0.47
Medical history, n (%)			
Stroke	7 (20)	12 (32)	0.29
High blood pressure	18 (51)	19 (51)	1.0
Diabetes mellitus	7 (20)	6 (16)	0.76
Any disease contraindicating organ donation	5 (14)	6 (17)	1.0
Prior treatment, n (%)			
Platelet aggregation inhibitor	11 (31)	7 (19)	0.28
Anticoagulation	10 (29)	9 (24)	0.79
Admission from, n (%)			0.82
Medical mobile emergency units	18 (51)	21 (57)	
Local emergency ward	14 (40)	14 (38)	
Other ward	3 (9)	2 (5)	
Glasgow Coma Scale			
Initial	7 (5–11)	7 (5–11)	0.71
Just before intubation	5 (4–6)	5 (4–7)	0.73
Treatment started before admission to ICU, n (%)			
Mechanical ventilation	29 (83)	36 (97)	0.06
Sedatives	24 (69)	20 (54)	0.24
Reason for intubation, n (%)			0.11
Comatose state	34 (97)	31 (84)	
Status epilepticus	1 (3)	6 (16)	
Time from the ICH onset, h			
To intubation	2 (1–3)	2 (1–3)	0.33
To admission to ICU	4 (3–7)	3 (3–6)	0.79
Physical examination at the admission			
Temperature, °C	36.1 (35.5–37.2)	37.0 (35.8–37.8)	0.11
Systolic arterial pressure, mmHg	170 (123–195)	172 (132–194)	1
Diastolic arterial pressure, mmHg	80 (62–101)	88 (69–110)	0.18
Neurological examination at the admission:			
Areactive comatose state*, n (%)	20 (57)	11 (30)	0.03
Motor response of the Glasgow Coma Scale	1 (1–2)	1 (1–2)	0.86
Eye response of the Glasgow Coma Scale	1 (1–1)	1 (1–1)	0.96
Pupil size, n (%)			0.02
Normal	4 (11)	12 (32)	
Anisocoria	10 (29)	8 (22)	
Bilateral miosis	9 (26)	14 (38)	
Bilateral mydriasis	12 (34)	3 (8)	
Pupillary light response, n (%)			<0.001
None	28 (80)	18 (49)	
Unilateral	4 (11)	2 (5)	
Normal	3 (9)	17 (46)	
Corneal reflexes, n (%)			<0.001
None	21 (60)	6 (16)	
Unilateral	6 (17)	5 (14)	
Normal	8 (23)	26 (70)	
Horizontal oculocephalic response, n (%)	11 (31)	29 (78)	<0.001
Cough response, n (%)	16 (46)	31 (84)	0.001
Spontaneous ventilation, n (%)	23 (66)	35 (95)	0.003
Number of abolished brainstem responses†	3 (2–4)	1 (0–2)	0.001
ICH score	4 (3–4)	3 (3–4)	0.15
Simplified Acute Physiology Score II	63 (57–75)	56 (52–59)	0.01

Table 1. continued

Variables	Evolution toward brain death: Yes (n = 35)	No (n = 37)	P-value
Biological characteristics			
Glycemia, g/l	2.18 (1.58–2.68)	2.32 (1.80–2.86)	0.92
Natremia, mmol/l	138 (136–141)	139 (136–140)	0.88
Creatininemia, μmol/l	80 (60–111)	88 (69–141)	0.37
PaO_2/FiO_2	334 (250–415)	345 (267–424)	0.70
International normalized ratio	1.18 (1.01–2.40)	1.10 (1.0–1.45)	0.41
Activated partial-thromboplastin time ratio	1.06 (0.90–1.41)	0.93 (0.85–1.12)	0.11
Platelet, G/l	198 (158–251)	240 (200–286)	0.08
Coagulation disorder, n (%)	23 (66)	17 (50)	0.11
Characteristics on the first CT scan			
Time from the ICH onset to CT, h	2 (2–3)	2 (2–3)	0.80
Location of intracerebral hemorrhage‡, n (%)			
Supratentorial	26 (74)	31 (84)	0.39
Infratentorial	11 (31)	9 (29)	0.39
Bilateral hemorrhage	10 (29)	9 (24)	0.79
Volume of intracerebral hemorrhage, cm^3	87 (25–140)	67 (23–101)	0.25
Peri-intracerebral hemorrhage edema, n (%)	32 (91)	33 (89)	1.0
Swirl sign, n (%)	26 (74)	10 (27)	<0.001
Intraventricular hemorrhage, n (%)	28 (80)	29 (78)	1.0
Intraventricular hemorrhage score	8 (1–10)	6 (1–10)	0.55
Brain herniation, n (%)			
Subfacial	24 (69)	24 (65)	0.81
Uncal	24 (69)	21 (57)	0.34
Cerebellar tonsillar	12 (34)	4 (11)	0.03

Continuous variables are expressed as medians and interquartile intervals. Categorical variables are expressed as numbers and percentages.
*Areactive comatose state is defined by a Glasgow Coma Scale score of 3.
†Five brain stem responses were evaluated at the admission to the intensive care unit: pupillary light response, corneal reflexes, horizontal oculocephalic response, cough response, and spontaneous ventilation. Pupillary light response and corneal reflexes were considered abolished in case of bilateral abolition.
‡Not mutually exclusive.

calculated by attributing one point for unilateral abolition of corneal reflexes, two points for bilateral abolition of corneal reflexes, and two points for the swirl sign. Patient scores are summarized in Table 3. The AUROC for Score 1 and for score 2 were similar: 0.85 vs. 0.84, (P = 0.90).

From these two models, we finally retained a simple three-group classification of BD risk from Model 2: low risk (no corneal reflexes abolition at ICU admission and no swirl sign on the first CT scan), high risk (at least one corneal reflex abolished at ICU admission and swirl sign on the first CT scan), and intermediate risk of ICH (the other patients; Fig. 2). Using this novel method, 5/9 ICU survivors would have been classed as at low risk of BD and 4/9 would have been classed as at intermediate risk of BD.

The swirl sign was the variable that was most predictive of BD on the first CT scan. We detected good inter-rater agreement for the swirl sign assessment (κ = 0.75). The Fig. 3 shows examples of baseline CT scans with and without swirl sign. The delay between the ICH onset and the CT scan realization was similar for the ICH with the swirl sign [1 (1–2) h] and for those without [1 (1–1.25) h, P = 0.28]. The mean volume of ICH with swirl sign was larger than for ICH without (109 cm^3 vs. 67 cm^3; P = 0.02). When we set 30 cm^3 as the threshold volume associated with worse prognosis in the ICH score [31,32], 27/36 (75%) ICHs with the swirl sign had a volume ≥ 30 cm^3 versus 20/27 (56%) of ICHs without (P = 0.14). The score then predicted BD with 96% sensitivity and 61% specificity for ICH ≥ 30 cm^3 and with 73% sensitivity and 71% specificity for ICH <30 cm^3 (Youden index not significantly different; P = 0.55).

Of the five brainstem reflexes collected at admission, the abolition of corneal reflexes was the variable most predictive of BD. Most patients (90%) had been placed under mechanical ventilation by medical mobile emergency units or in the local emergency ward, and sedatives (midazolam with or without sufentanil) had been started in 61% of patients before admission to ICU. Therefore, as the administration of sedatives could have influenced the neurological examination upon ICU admission, we assessed the score's ability to accurately predict BD in

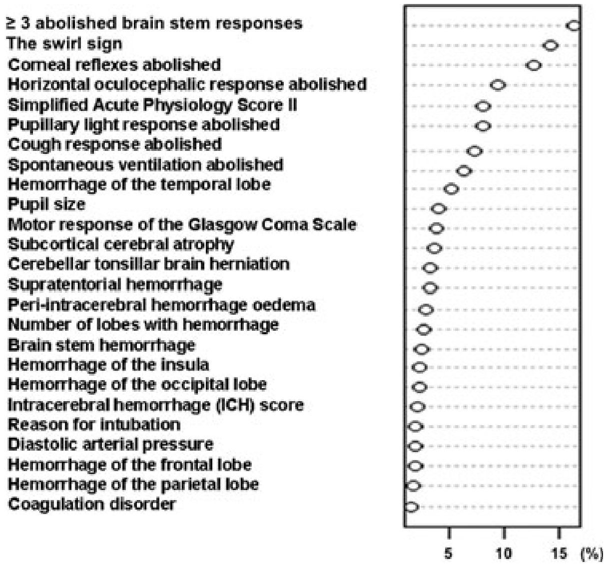

Figure 1 Absolute decrease in the percentage of accurate patient predictions after random permutation of the corresponding variable among patients (the random forest method). The larger the decrease, the more the variable contributes to the accuracy of the prediction of BD.

Table 2. Two models to predict upon admission evolution toward brain death.

Variable	Crude odds ratio	Adjusted odds ratio	*P*-value
Model 1			
Number of abolished brainstem responses ≥3	12.3 (3.8, 39.6)	8.4 (2.4, 29.1)	<0.0001
The swirl sign	7.8 (2.7, 22.3)	5.0 (1.6, 15.9)	0.006
Model 2			
Abolition of corneal reflexes			0.002
Unilateral	3.9 (0.9, 16.3)	4.2 (0.9, 20.1)	
Bilateral	11.4 (3.4, 37.9)	8.8 (2.4, 32.3)	
The swirl sign	7.8 (2.7, 22.3)	6.2 (1.9, 20.0)	<0.0001

patients who received sedatives before admission to ICU versus patients who did not. The score including corneal reflexes and the swirl sign predicted BD with 88% sensitivity and 60% specificity for patients who received sedatives and with 91% sensitivity and 70% specificity for patients who did not (Youden index not significantly different; $P = 0.46$). Similarly, the abolition of corneal reflexes may have different ramifications in patients with infratentorial ICH than in patients without. The score predicted BD with 73% sensitivity and 67% specificity for patients with infratentorial ICH and with 96% sensitivity and 64% specificity for patients without (Youden index not significantly different; $P = 0.37$).

Discussion

We report here the first investigation in which variables collected upon ICU admission are demonstrated to be predictive of BD in comatose patients with ICH. Moreover, we propose a simple tool to help intensivists and neurologists stratify patients according to the risk of BD.

To date, very few studies have focused on patients with ICH to identify variables that are predictive of BD. Dominguez-Roldan *et al.* [39] compared CT scans of patients with ICH who evolved to BD with survivors and reported that, in patients who evolved to BD, the mean midline shift and the volume of supratentorial ICH were significantly higher than in survivors, and the mesencephalic/pontine and the internal capsulae/putamen locations, uncal brain herniation, and compression of the fourth ventricle were more frequent than in survivors. However, patients who evolved to BD were only compared with patients who survived; the study excluded patients who died without evolving to BD. Therefore, it is uncertain how useful these data are accurately predicting BD. Moreover, the swirl sign was not assessed in this study. Zurasky *et al.* [10] found that patients with ICH who evolved to BD had a lower median admission Glasgow Coma Scale score (without defining a threshold), and that African-American patients evolved more often to BD and were less concerned by early decisions to withdraw life support. Some experts have recently proposed definitions of imminent BD based on abolished brain stem responses [17,18]. Recently, analyzing patients who died on an ICU in Dutch university hospitals, it has been reported that 45.6% of patients with imminent BD actually evolved toward BD [19]. The aim of this study was not to identify predictors of evolution toward BD as early as possible. It has to be noticed that the accuracy of this imminent BD definition has not been evaluated upon the admission to ICU, but at any moment during the ICU stay [19]. Moreover, using our simple three-group classification of BD risk upon the admission to ICU based on the corneal reflexes abolition and the swirl sign, 83% of patients with high risk of BD and 50% of patients with intermediate risk of BD actually evolved toward BD. Therefore, our study is the first to identify simple and discriminating variables that predict BD in comatose patients with ICH upon admission.

The mortality rate of our patients is consistent with the literature for patients with very high ICH scores, a comatose state requiring mechanical ventilation, and admission to the ICU after having been denied admission to a neurosurgical ICU [31,32]. The percentage of patients who evolved toward BD in our study is close to the higher reported rates [8–10]. The short length of stay in ICU before patients evolved to BD is in accordance with other studies [8,40].

Table 3. Two scores predicting evolution toward brain death.

	Score 1*			Score 2†		
Value of the score	0	1	2	0–1	2	3–4
Number of patients, *n*	29	22	21	28	20	24
Evolution to brain death, *n* (%)	4 (14)	13 (59)	18 (86)	4 (14)	11 (55)	20 (83)
Threshold	≥ 1			≥ 2		
Sensitivity	0.89			0.88		
Specificity	0.68			0.65		
Positive predictive value	0.72			0.70		
Negative predictive value	0.86			0.86		

*The score 1 was calculated by attributing one point for ≥ 3 abolished brain stem responses upon admission to the ICU and one point for the swirl sign on the first CT scan.

†The score 2 was calculated by attributing one point for unilateral abolition of corneal reflexes, two points for bilateral abolition of corneal reflexes upon admission to the ICU and two points for the swirl sign on the first CT scan.

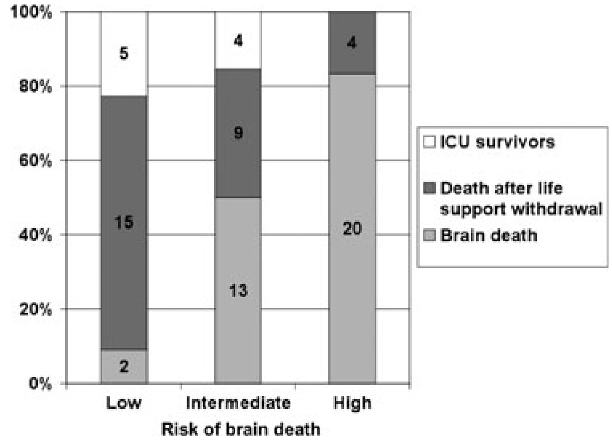

Figure 2 Classification of risk of BD in three groups, as derived from Model 2. The three groups were defined as follow: low risk (no corneal reflexes abolition at ICU admission and the swirl sign on the first CT scan), high risk (at least one corneal reflex abolished at ICU admission and the swirl sign on the first CT scan), and intermediate risk of ICH (the other patients).

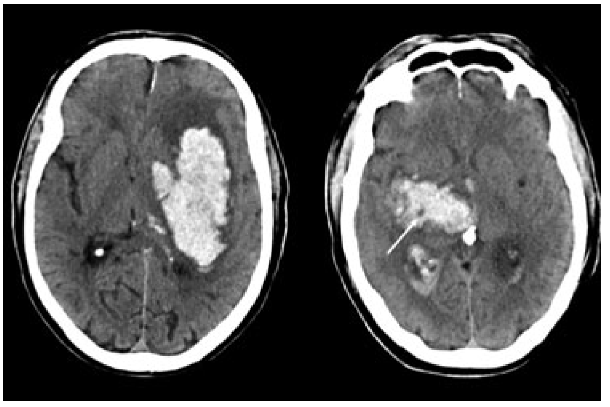

Figure 3 Examples of baseline unenhanced CT scans. Left: intracerebral hemorrhage without swirl sign. Right: the swirl sign represents actively extravasating unclotted fresh blood (arrow) which is of lower attenuation than clotted blood (typically 50–70 HU) which surrounds it. It represents active bleeding in the hematoma.

One of the strengths of our study is that we usually do not make early do-not-resuscitate orders or early decisions to withdraw life support. Physicians often underestimate the outcome of patients with ICH [41], and these "self-fulfilling prophecies" may impact patient outcome [42]. Early decisions to limit or to withdraw life support have been identified as a major risk of death in patients with ICH [16]. Given that the lengths of stay in the ICU of patients who died from BD and patients who died after withdrawal of life support were 2 (2–3) days and 7 (5–9) days, respectively, we suggest that our local practice of withdrawal of life support did not introduce bias by preventing evolution toward BD.

Abolition of ≥ 3 brainstem responses upon admission was the most discriminating variable for the prediction of BD. All current proposed definitions of imminent BD are based on the loss of brainstem reflexes [17,18]. Of the set of brainstem reflexes tested upon admission, we found that the abolition of corneal reflexes was most predictive of BD, and that its predictive value did not differ according to whether the ICH was infratentorial. Sharshar *et al.* [43] recently reported the neurological examination of sedated (by midazolam with or without sufentanil) patients admitted to the ICU without neurological disease [43]; corneal reflexes were abolished in <10% of sedated patients, and other brainstem reflexes were abolished in 20–50% of them [43]. Considering that 61% of our patients had received midazolam with or without sufentanil before admission to the ICU, we speculate that the minor effect of these sedatives on the corneal reflexes may explain why the abolition of these reflexes was the variable most predictive of BD. Moreover, we confirmed that the predictive value of the abolition of corneal reflexes did not vary according to whether the patient had received sedatives prior to admission. The score including corneal reflexes and the swirl sign predicted BD with similar accuracy whether the patients received sedatives prior to admission or not.

As we focused on comatose patients with ICH who required mechanical ventilation, it is not surprising that characteristics on the first CT scan usually associated with poor outcome in the literature (such as large ICH or associated intraventricular hemorrhage) were very common in our patients [13,14]. In our study population, the swirl sign was the element of the first CT scan that was most predictive of BD with a good inter-rater agreement. The swirl sign seen on unenhanced CT scans represents active bleeding in the hematoma. It represents actively extravasating unclotted fresh blood which is of lower attenuation than clotted blood (typically 50–70 HU) which surrounds it [27–30]. Pathological studies have shown that multiple bleeding areas arising from ruptured arterioles or venules may explain early ICH growth [7, 44]. This swirl sign has first been described in patients with head trauma who have an acute epidural hematoma containing both a hyperattenuating clot and a smaller hypoattenuating region [28,45]. This hypoattenuating area has been shown to correspond to active bleeding sites at the time of surgery [27, 28]. Using the placebo data set from the proof-of-concept trial of recombinant activated Factor VII for ICH [46], Barras *et al.* showed that baseline volume and ICH growth at 24 h were higher in the heterogeneous ICH (with swirl sign) than in the homogeneous ICH (without swirl sign) [29]. In multivariate analysis, it underwent significantly greater mean growth after adjustment for baseline ICH volume and time to CT scan [29]. ICH growth is highly predictive of neurological deterioration and is an independent predictor of mortality and functional outcomes [7,42,47–52][14]. When baseline CT scan is performed within 3 h of onset, ICH growth >33% occurs in 38% of patients [48], and the earlier the first CT scan, the more likely it is that ICH growth will occur [53,54]. The organization of our local emergency ward, as well as the medical mobile emergency units that promptly bring patients in a comatose state to a neurosurgical unit for CT, explains the early implementation of CT scan (75% of the CT scan were performed within 3 h of onset). Therefore, we hypothesize that the swirl sign predicts early ICH growth leading to increasing intracranial pressure, decreasing cerebral perfusion pressure, and BD. Kim *et al.* found that the swirl sign in ICH was associated with 30-day mortality, without precising the rate of BD [30]. The swirl sign of ICH on unenhanced CT scans is the corollary of the spot sign on enhanced CT scans which represents the same phenomenon, but in that case caused by contrast extravasations and is also clearly associated with early ICH growth and mortality [30,55–57]. Only five studied patients had a baseline unenhanced and enhanced CT scans, one of them had a spot sign and evolved toward BD. However, we cannot assess if the spot sign predicts BD. Most of these studies aimed to identify predictors of early ICH growth to propose treatments to prevent it [7]. We think that further studies which aim to precise prognosis of ICH or predictors of ICH growth should precise the rate of patients dying from BD.

We also note several limitations of the present study. First, this is a retrospective study. Data from the admitting neurological examination were collected from patient charts. We were unable to obtain data on other brainstem reflexes than those reported, such as the oculovestibular and gag reflexes, because they were often not tested at the admission. Second, to homogenize the study population, we limited our analysis to patients admitted for severe spontaneous ICH with coma. The main reason of this deliberate choice to focus on comatose patients was that they represent the population in whom the justification of admission to ICU is questionable in the literature. In the real life, the admission to ICU (or Neuro-ICU) of noncomatose patients with ICH is already a widespread practice because the objective is curative. But, in case of ICH with severe coma, physicians face everyday a difficult ethical decision regarding the admission to ICU and the placement under mechanical ventilation. On the one hand, introduce or pursue full supportive care in these patients with very high predicted mortality could lead to futile prolongation of life; on the other hand, deny their admission to ICU could miss evolution toward BD and organ donation, increasing the shortage of organs available for transplantation. We decided to focus on patients with ICH because they represent the primary source of organ donation in France and because we planned to identify parameters on the first CT scan which could identify patients who will evolve toward BD. It would have been much more difficult if we had included in the analysis patients with ischemic stroke or isolated subarachnoid hemorrhage for example. We recommend a similar analysis of patients with a better state of consciousness or with other neurological diseases to precise if the identified parameters could be useful in a much broader population. In addition, all of our patients had been denied admission to a neurosurgical unit, and thus extrapolation of our results to patients who have undergone external ventricular drainage or surgical evacuation of the hematoma should be undertaken with caution.

Conclusions

We have identified the simple clinical and radiological signs evaluated upon admission to the ICU that predict BD in comatose patients with spontaneous ICH. These results should assist intensivists and neurologists in their difficult decision to introduce or pursue full supportive care in comatose patients with ICH and very high predicted mortality. Early identification of patients who will probably evolve toward BD could allow their admission to ICU whereas the opposite decision could have worsened the shortage of organs donation. We hope that these results could increase the number of potential heart-beating donors.

Authorship

AG: wrote the manuscript, designed the study, collected, and analyzed data. PYB: analyzed data. EH, MR, JC: collected radiological data. JLB, HAO, MA, NB: collected clinical and biological data. EM and BG: designed the study. GO: wrote the manuscript and designed the study.

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