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Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorrain, France

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Summary

There are no established predictive factors to identify patients at the acute phase of severe stroke with a high probability of presenting brain death (BD). We retrospectively collected clinical and paraclinical data of consecutive patients at the acute phase of severe stroke with a potential progression to BD through the hospital organ procurement and transplant coordination system in five centres in Lorrain (France) between 1 January 2012 and 31 December 2013. Final endpoint was adjudicated BD. Of 400 included patients, 91 (23%) presented adjudicated BD. Initial Glasgow Coma Scale score ≤6 ($P = 0.008$), herniation ($P = 0.009$), hydrocephalus ($P = 0.019$), initial systolic blood pressure >150 mmHg ($P = 0.002$), past history of alcohol abuse ($P = 0.019$) and stroke volume >65 ml ($P = 0.040$) were significantly associated with BD progression. Two prognostic scores for stroke with unquantifiable or quantifiable volume were built according to the number of risk factors presented. Following internal validation, the respective bias-corrected predictive performance (c-index) of the two scores was 72% (95% confidence interval: 67–78%) and 77% (95% confidence interval: 72–82%). These scores could form the basis of a simple tool of six criteria to help physicians make the difficult decision of intensive care unit management to preserve organs in potential donors.

Introduction

Patients with severe brain injuries are most likely to progress to brain death (BD) [1]. A French register conducted by the 'Agence de la Biomédecine' revealed that stroke was the first cause of progression to BD and accounted for around 58% of organs available for donation in France in 2013. Potential donors require intensive care unit (ICU) management to preserve organs until possible BD. However, identifying patients with severe stroke which could progress to BD is particularly difficult at the acute phase because of a lack of clearly established predictive clinical or paraclinical criteria. Previous studies have identified simple predictive clinical signs for BD in comatose patients but only following haemorrhagic strokes or traumatic brain injuries which are not representative of the population of patients in stroke units [2,3]. In practice, physicians do not have a reliable tool to predict BD which results in a failure of screening potential organ donors among stroke patients and a risk of inflicting invasive resuscitation measures to protect the organs in patients with a low probability of BD. Determining the predictive factors of BD could help physicians to better identify potential organ donors and to make the difficult choice between management in ICU and a withholding and withdrawing decision. We designed a study to determine predictive clinical and paraclinical factors of BD in stroke victims at admission and to establish a simple score usable in clinical practice.

Patients and methods

We conducted a multicentre observational retrospective cohort study in five centres in Lorrain (north-eastern France). The study addressed all stroke patients hospitalized between 1 January 2013 and 31 December 2013 with a no-therapy decision and a likely prognosis of progression to BD. These patients were identified by the hospital organ procurement and transplant coordination (OPTC) according to the French program for the identification of comatose patients admitted in hospital.

Patients

The inclusion criteria were the presence of a recent stroke (haemorrhagic or ischaemic) and/or subarachnoid haemorrhage (SAH) on brain imaging (CT scan or MRI) and selection by OPTC after no-therapy decision for likely poor outcome. The decision to withhold therapy had to be made collegially according to ethical and legal guidelines. The decision of whether to call the OPTC was up to the physician based on if he/she considered that the severity of the stroke could progress to BD.

Data collection

An investigator in each hospital collected baseline demographic, clinical and paraclinical data by means of a standardized form. A login number was assigned for each patient to ensure anonymity. The following data were collected as follows: age, sex, systolic (SBP) and diastolic blood (DBP) pressure at admission, personal cardiovascular risk factors (high blood pressure, excessive alcohol consumption, diabetes, dyslipidemia and atrial fibrillation), Glasgow Coma Scale (GCS) score before sedation, anticoagulant treatment, antiplatelet therapy and intravenous thrombolytic therapy. All brain CT scans and MRI were similarly collected and transferred to the Neurology Department of the University Hospital of Nancy. Type of stroke (haemorrhagic or ischaemic), subtype (ischaemic, parenchymal haematoma (PH), SAH only or PH with SAH), stroke volume (for ischaemic stroke and PH, SAH and vertebrobasilar infarctions were excluded) assessed by a thresholding method, location (supra- or infratentorial), evidence of herniation, the presence of intraventricular haemorrhage, the presence of hydrocephalus, vascular territory for ischaemic stroke (vertebrobasilar or anterior), anatomical location of PH (lobar, profound or brainstem) and Fischer scale for SAH were determined from MRI analysis. The images were systematically inspected for subfalcine, uncal transtentorial and foraminal herniations which were recorded without distinction. Hydrocephalus was defined as 'increased radius or decreased ventricular angle in frontal horns, rounding and enlargement of atrium with sulcal effacement, increased width of third ventricle, or ballooning of fourth ventricle' [4]. Physicians analysing the MRI data were kept unaware of the patient's status (BD or not). 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).

Follow-up

After inclusion in the study, patients were followed up until BD, death by another cause or until they left the ICU (good outcome). Each case of BD was confirmed by two medical clinical examinations meeting the mandatory criteria of the current French legislation for organ procurement. These examinations comprised: two electroencephalography recordings of 30 min performed 4 h apart demonstrating electrocerebral inactivity, the absence of intracerebral filling at the level of the carotid bifurcation or circle of Willis by CT scan and apnoea testing [5]. The endpoint was BD determined clinically in accordance with the mandatory criteria (adjudicated BD) for organ donation.

Statistical methodology

All analyses were carried out using SAS R9.3 (SAS Institute, Cary, NC, USA). The two-tailed significance level was set at $P < 0.05$. Continuous variables were described as mean $\pm$ standard deviation, categorical factors as frequency and percentage. Pairwise comparisons were performed using Student's *t*-test and chi-square test as appropriate. Associations between outcomes (adjudicated BD) and baseline characteristics were identified using a two-step logistic regression: significant factors at the $P < 0.20$ level were first selected from bivariate analyses and then entered in a multivariable model. As the study aimed to determine a convenient predictive score of BD, continuous characteristics were converted into binary risk factors prior to analysis using the cut-points maximizing at best sensitivity and specificity according to ROC analysis (Youden's index criterion). Final multivariable logistic models retained only factors found significant at the $P < 0.05$ level using a stepwise forward/backward selection method; the validity assumptions of the models (the absence of collinearity and interaction, goodness of fit) were thoroughly checked. Two sets of candidate characteristics were identified: the first for stroke-type-independent factors (evaluable in all patients: SBP/DBP, history of hypertension, diabetes, alcohol abuse, GCS, hydrocephalus and herniation – age was not considered because age-linked confounding characteristics such as cerebral atrophy

decreasing the risk of intracranial hypertension could modify the prognosis of older patients) and the second for stroke-type-dependent factors (location relative to the tentorium, intraventricular haemorrhage and stroke volume, respectively, not quantifiable in SAH, ischaemic stroke and SAH/vertebrobasilar infarction). A first predictive model ('model 1') was built using the stroke-type-independent factors, on top of which stroke-type-dependent factors were assessed in a second model ('model 2'). The logistic regression results were presented as number of BD/number of patients, odds ratio (OR), OR 95% confidence interval (95% CI) and *P*-value. The performance of the models was assessed using Harrell's c-index (area under the ROC curve C0), which is the probability of correctly predicting the occurrence of the outcome in the sample. Internal validation was performed using the bootstrap method described by Harrell *et al.* [6] on 1000 bootstrap samples. Briefly, 1000 random samples of the same size as the original sample were generated with replacement (a same observation may be repeated several times in the bootstrap sample). In each of the generated samples, a logistic model was fitted using the same selection procedure as in the original model including a novel determination of cut-points for continuous characteristics, giving a first c-index C1. This model was then applied to the original sample, giving a second c-index C2. The difference C1-C2 averaged over the 1000

Table 1. Clinical and radiological characteristics of patients according to brain death status.

Factors	No adjudicated brain death *n* = 309	Adjudicated brain death *n* = 91	All patients *n* = 400	*P*-value
Demographic characteristics				
Age (years)	70 ± 16	66 ± 16	68 ± 16	0.030
Male gender	143 (46)	46 (50)	189 (47)	0.47
Cardiovascular risk factors				
Hypertension	198 (64)	51 (56)	249 (62)	0.16
Dyslipidemia	75 (24)	22 (24)	97 (24)	0.98
Atrial fibrillation	76 (25)	19 (21)	95 (24)	0.46
Alcohol abuse	38 (12)	22 (24)	60 (15)	0.005
Diabetes mellitus	60 (19)	10 (11)	70 (17)	0.062
Clinical characteristics				
Systolic BP (mmHg)	307 (156 ± 33)	90 (167 ± 34)	397 (161 ± 33)	0.002
Diastolic BP (mmHg)	307 (85 ± 19)	90 (91 ± 20)	397 (88 ± 19)	0.009
GCS	301 (7 ± 3)	90 (6 ± 2)	391 (6 ± 2)	0.001
Stroke characteristics				
Stroke type				
Haemorrhagic	222 (72)	71 (78)	293 (73)	0.24
Ischaemic	87 (28)	20 (22)	107 (27)	
Stroke subtype				
SAH	39 (13)	12 (13)	51 (13)	0.64
PH	163 (53)	50 (55)	213 (53)	
Infarct	82 (26)	19 (21)	101 (25)	
SAH+PH	25 (8)	10 (11)	35 (9)	
Stroke location				
Supratentorial	233 (86)	61 (77)	294 (84)	0.051
Infratentorial	37 (14)	18 (23)	55 (16)	
Herniation	89 (30)	51 (57)	140 (36)	0.0001
Hydrocephalus	114 (38)	58 (65)	172 (44)	0.0001
Intraventricular haemorrhage	159 (73)	63 (90)	222 (77)	0.002
Antithrombotic drugs				
Vitamin K antagonists	39 (18)	15 (21)	54/289 (19)	0.50
INR	3.5 ± 1.4	3.6 ± 1.4	3.5 ± 1.4	0.60
Direct anticoagulants	3 (1)	1/71 (1)	4/293 (1)	0.97
Single antiplatelet therapy	74 (34)	25/70 (36)	99/290 (34)	0.75
Double antiplatelet therapy	7 (3)	2/70 (3)	9/290 (3)	0.89
Thrombolysis	12 (4)	6 (7)	18 (5)	0.27

BP, blood pressure; GCS, Glasgow Coma Scale; SAH, subarachnoid haemorrhage; PH, parenchymal haematoma; INR, international normalized ratio. Figures are mean ± standard deviation or frequency (percent), and percentages were computed, respectively, in haemorrhagic and ischaemic stroke subgroups for antithrombotic drugs, *P*-values from Student's *t*-test or chi-square test when appropriate.

bootstrap samples represents the best estimation of the bias (overfitting) of the initial model, which is then subtracted from the initial c-index. The predictive performance of the models is expressed as the resulting bias-corrected c-index and its 95% CI computed from the 1000 bootstrap samples.

Results

Four hundred stroke patients were identified by OPTC as potential organ donors, among whom only seven more than 24 h after stroke onset. Ninety-one (23%) progressed to adjudicated BD, and organ donation was performed in 52 (13%) cases. The average age of the 91 patients progressing to BD was 66 years (range 18–92), 50% were male, mean SBP/DBP values were 167/91 ± 34/20 mmHg, GCS score was 6 ± 2, and cerebral lesions were haemorrhagic in 78%. Patients and stroke characteristics are presented in Table 1. The factors significantly associated with BD in bivariate analysis are presented in Table 2. The first multivariate analysis testing stroke-type-independent characteristics identified five significant factors associated with BD risk (87 BD in 377 patients): GCS score ≤6 ($P = 0.008$), hydrocephalus ($P = 0.019$), herniation ($P = 0.009$), initial SBP >150 mmHg ($P = 0.002$) and alcohol abuse ($P = 0.019$): these five factors were selected by 59 (alcohol abuse) to 86% (SBP) of the 1000 bootstrap replications. The estimated bias of the model was 3.5% and the corrected c-index 70% (63–77%). Mean cut-points resulting from internal validation were 6 for

Table 2. Association between baseline characteristics and progression to brain death.

Factor	Events/patients	Units	OR (95% CI)	*P*
Clinical characteristics				
Male gender	91/400	Yes vs. no	1.19 (0.74–1.89)	0.47
Age				
Continuous (years)	91/400	Per 5 years	0.93 (0.86–0.99)	0.033
Age ≤80 years	91/400	Yes vs. no	2.21 (1.25–3.89)	0.006
SBP				
Continuous	90/397	Per 10 mmHg	1.12 (1.04–1.20)	0.002
>150 mmHg	90/397	Yes vs. no	2.36 (1.41–3.94)	0.001
DBP				
Continuous	90/397	Per 10 mmHg	1.17 (1.04–1.33)	0.010
>95 mmHg	90/397	Yes vs. no	2.18 (1.34–3.57)	0.002
Thrombolysis	91/400	Yes vs. no	1.75 (0.64–4.79)	0.28
Past history				
Atrial fibrillation	91/400	Yes vs. no	0.81 (0.46–1.43)	0.46
Hypertension	91/400	Yes vs. no	0.71 (0.44–1.15)	0.17
Diabetes	91/400	Yes vs. no	0.51 (0.25–1.05)	0.067
Dyslipidemia	91/400	Yes vs. no	0.99 (0.58–1.72)	0.99
Alcohol abuse	91/400	Yes vs. no	2.27 (1.26–4.09)	0.006
Stroke characteristics				
Type independent				
GCS before sedation				
Continuous	90/391	Per grade	0.85 (0.77–0.94)	0.002
GCS ≤6	90/391	Yes vs. no	2.17 (1.31–3.59)	0.003
Stroke type	91/400	Isch. vs. haemo.	0.72 (0.41–1.25)	0.24
Hydrocephalus	89/390	Yes vs. no	3.07 (1.87–5.03)	<0.0001
Herniation	90/390	Yes vs. no	3.10 (1.91–5.04)	<0.0001
Type dependent				
Supratentorial location	79/349	Yes vs. no	1.86 (0.99–3.49)	0.054
IV haemorrhage	70/290	Yes vs. no	3.45 (1.50–7.95)	0.004
Vascular territory	19/99	Ant. vs. vert.	0.99 (0.29–3.37)	0.98
PH/CI volume				
Continuous	78/337	Per 10 ml	1.05 (1.02–1.07)	0.001
>65 ml	78/337	Yes vs. no	4.92 (2.79–8.68)	<0.0001

OR (95% CI), odds ratio (95% confidence interval); *P*, *P*-value from logistic regression; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; isch., ischaemic, haemo., haemorrhagic; IV, intraventricular; ant., anterior territory; vert., vertebrobasilar territory; PH, parenchymal haematoma; CI, cerebral infarction.
Bivariate logistic regression, events: brain deaths.

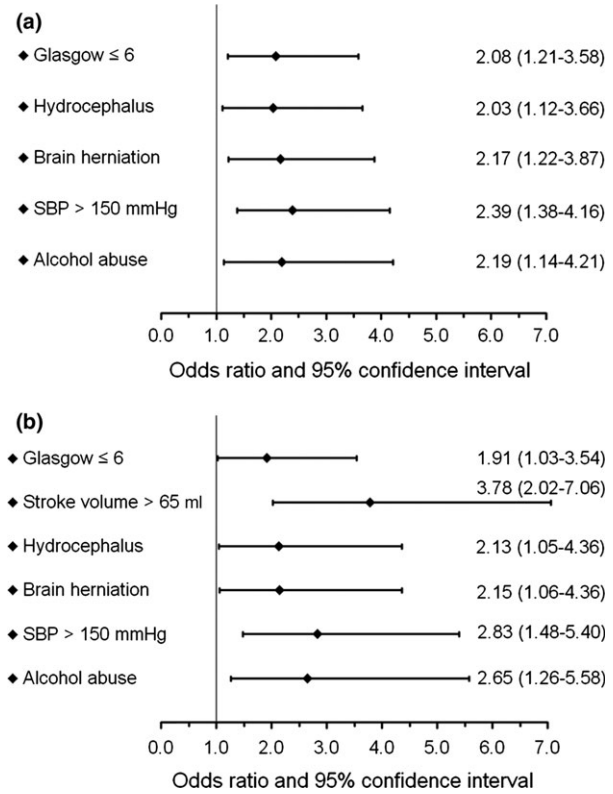

Figure 1 Factors significantly associated in multivariate analysis with progression to brain death for model 1(a) and 2(b), odds ratio and 95% confidence interval. Model 1: stroke-type independent, model 2: stroke-type dependent, SBP: systolic blood pressure.

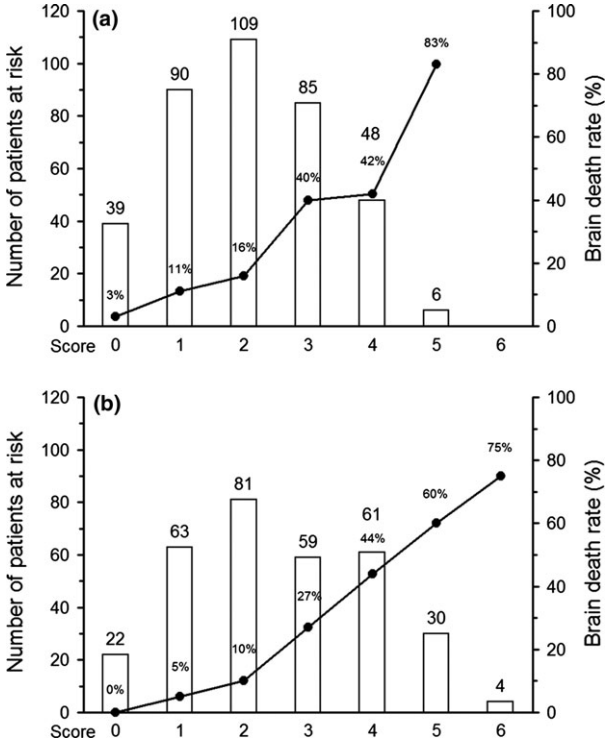

Figure 2 Number of patients at risk and the percentage of progression to brain death at each point of scores for model 1(a) and 2(b). Model 1: stroke-type independent (without stroke volume), model 2: stroke-type dependent (with stroke volume).

GCS and 155 mmHg for SBP. As all factors had similar ORs close to 2 (Fig. 1a), a first score was built in which each factor counted for 1 point when present. The distribution of the number of factors in the sample was approximately bell-shaped, while the BD rate increased exponentially (Fig. 2). The resulting scores were then grouped in three approximatively equal-sized classes: grade 1 (0–1 factors, 129 patients), grade 2 (2 factors, 109 patients) and grade 3 (3–5 factors, 139 patients) (Fig. 3a). This resulted in a 3-level score, (Table 3, Score 1), where the risk of BD in grade 2 was twice as high as in grade 1 ($P = 0.096$), and 8 times higher in grade 3 ($P < 0.0001$). The bias-corrected c-index of the score was 72% (67–78%). The risks derived from bootstrap internal validation were (mean and 95% CI) 8% (4–13%), 16% (9–23%) and 42% (34–50%) for grades 1, 2 and 3, respectively. The sensitivity and specificity of each grade are presented in Table 4 (score 1). The small number of events in the reference grade (0-1 factors: 11/129) explains the large values of OR (95% CI) of grades 2 and 3.

The second multivariable analysis identified stroke volume >65 ml as an additional factor ($P = 0.040$) in patients with infarct or PH (Fig. 1b), despite the power loss due to a 15% smaller sample size (75 BD in 320 patients): this factor was selected in 99% of the 1000 bootstrap replications. The estimated bias of the model was 3.2%, its corrected c-index 80% (74–86%). Mean cut-points resulting from internal validation were 6 for GCS, 156 mmHg for SBP and 65 ml for stroke volume. The resulting scores were again grouped in three distinct classes: grade 1 (0–1 factor, 85 patients), grade 2 (2–3 factors, 140 patients) and grade 3 (4–6 factors, 95 patients) (Fig. 3b). This resulted in a 3-level score (Table 3, Score 2) where the risk of BD in grade 2 was six times higher than in grade 1 ($P = 0.006$), and 28 times higher in grade 3 ($P < 0.0001$). The bias-corrected c-index of the score was 77% (72–82%). The risks derived from bootstrap internal validation were (mean and 95% CI) 4% (0–8%), 17% (11–23%) and 50% (40–60%) for grades 1, 2 and 3, respectively. The sensitivity and specificity of each grade are presented in Table 4 (score 2).

Sensitivity analysis taking into account haemorrhagic damage only (i.e. excluding ischaemic strokes) did not reveal a significantly different predictive performance for the two models compared to the whole population (data not shown).

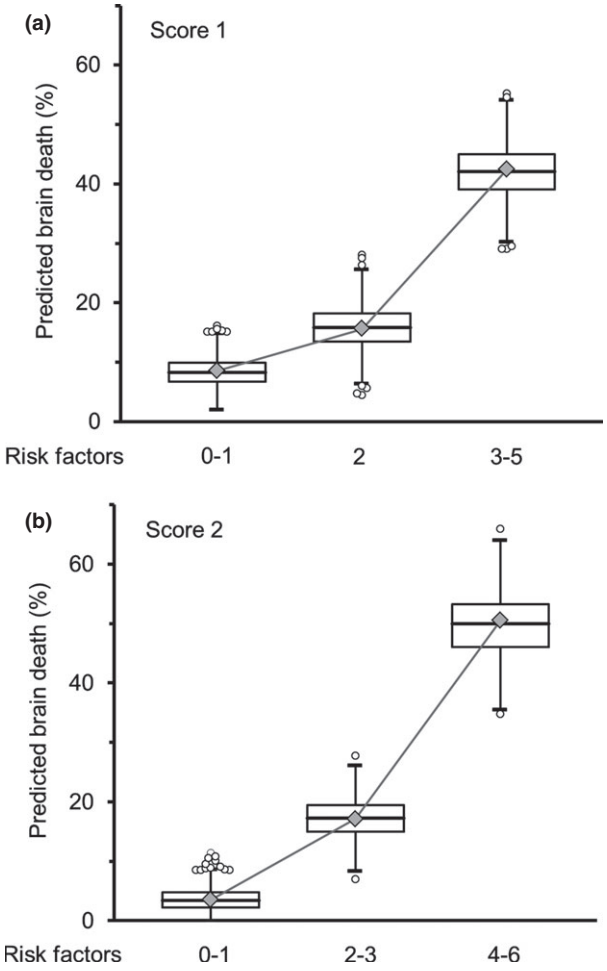

Figure 3 Predicted percentages of patients (Tukey's box and whiskers plots derived from internal validation) with brain death progression according to score for model 1(a) and 2(b). Model 1: stroke-type independent (without stroke volume), model 2: stroke-type dependent (with stroke volume), box limits: interquartile range (IQR), middle line: median, vertical lines: adjacent values (1st quartile − 1.5 IQR; 3rd quartile + 1.5 IQR), empty dots: outliers. Additional data: observed percentages of patients with progression to brain death (grey diamonds and corresponding curve).

Discussion

Stroke severity remains a subjective notion and is currently based on the physician's experience taking into account all the clinical and radiological signs which could predict a life-threatening condition for the patient. Objective tools to better define severity are required, all the more so in the case of a potential progression to BD. We have identified several predictive factors which could form a predictive score of BD in patients at the acute phase of severe stroke: GCS score ≤6 before sedation, stroke volume >65 ml, the presence of herniation and/or hydrocephalus on brain imaging, initial SBP >150 mmHg and history of alcohol abuse. These findings could form the basis of a simple score usable at the patient's bedside to help physicians identify patients likely to progress to BD. Nearly, all the patients in this study were identified by OPTC within 24 h following stroke onset, that is the interval we consider as being the acute phase during which our score would be applicable.

Several criteria have already been used to predict BD in patients with serious post-traumatic cerebral injuries in neurosurgical centres but not for stroke patients. Furthermore, while numerous studies describe criteria as factors of poor prognosis (functional and vital) in stroke patients – primary coma, National Institute of Health Stroke Score (NIHSS) >17 and stroke volume >60 cm^3 – they do not specifically focus on progression to BD [3]. Clinical grading scales play an important role in evaluating patients with acute neurological disorders and in their management. The impact of a low initial GCS score has been reported as a predictive factor of poor outcome in stroke patients and may reflect severe brain injury and hydrocephalus due to high stroke volume and herniation [3]. It should be systematically calculated at the first medical examination to evaluate the patient's neurological status. The NIHSS does not seem to be an appropriate indicator because of the quasi-systematic presence of coma on patient admission. In our study, high initial SBP is independently associated with

Table 3. Risk progression to brain death according to the number of predictive factors.

	Grade	Risk factors number	Interpretation	Events/patients	OR (95% CI)	*P*-value	Corrected c-index
Score 1	1	0 1 factor	–	11/129	Reference		72% (67–78%)
	2	2 factors	vs. 0–1 factor	17/109	1.98 (0.89–4.44)	0.096	
	3	3–5 factors	vs. 0–1 factor	59/139	7.91 (3.92–16.0)	<0.0001	
		Total	–	87/377	–	–	
Score 2	1	0 1 factor	–	3/85	Reference		77% (72–82%)
	2	2–3 factors	vs. 0–1 factor	24/140	5.66 (1.65–19.4)	0.006	
	3	4–6 factors	vs. 0–1 factor	48/95	27.9 (8.24–94.6)	<0.0001	
		Total	–	75/320	–	–	

Score 1: stroke-type independent (without stroke volume), score 2: stroke-type dependent (with stroke volume). OR (95% CI): odds ratio (95% confidence interval) and corrected c-index: bootstrap bias-corrected c-index (95% confidence interval).

Table 4. Sensitivity and specificity of the scores for brain death prediction.

	Grade	Risk factors number	Sensitivity, %	Specificity, %	Positive PV, %	Negative PV, %
Score 1	1	0 1 factor	13	59	8	70
	2	2 factors	20	69	16	74
	3	3–5 factors	67	72	42	88
Score 2	1	0–1 factor	4	66	4	70
	2	2–3 factors	33	53	17	72
	3	4–6 factors	63	81	50	88

PV, predictive value.
Score 1: stroke-type independent (without stroke volume), score 2: stroke-type dependent (with stroke volume).

progression to BD. High blood pressure is a known predictive factor of poor functional and vital outcomes, for both haemorrhagic and ischaemic strokes, but has yet to be proved as a predictive factor of BD [7]. The impact of stroke volume on BD in our study was clear: we were able to define a cut-off volume of 65 ml, a threshold above which patients are more likely to progress to BD. Earlier studies have already described criteria to predict progression of fatal brain swelling for anterior ischaemic strokes. They are in accordance with our study as stroke volume was one of the strongest predictors. Kriger *et al.* showed an independent association with mortality for hypodensity in more than half of the middle cerebral artery territory on CT scan, while Oppenheim *et al.* determined a cut-off of 145 ml on diffusion weighted images for malignant progression with a sensitivity of 100% [8,9]. Our score used a lower cut-point without reaching the same sensitivity. However, previous studies were more focused on predicting death, while our 65 ml cut-off reflects progression to BD in a widespread population. It should be noted that our volume was determined by combining PH and cerebral infarcts on CT scan and MRI. For haemorrhagic stroke, several studies have established a link between stroke volume and clinical outcome. A lower cut-off between 20 and 30 ml is more widely used to predict a high risk of short term mortality [10]. Hydrocephalus and herniation were also found associated with BD. This indirectly reflects a high stroke volume associated with a compression of vital vegetative centres in the brain. One study describes hydrocephalus as a predictor of early mortality in young patients with nontraumatic intracerebral haemorrhage [4]. Alcohol abuse has already been described as an aggravating factor of stroke, especially for PH, as it can increase SBP [11]. Finally, it was found to be significantly associated with BD in our study. Alcohol abuse was deduced from an interview with the patients' relatives and was retained if they considered the patient drank too much, too often or was unable to control his/her alcohol consumption. Future prospective studies should assess this factor with a more precise quantification of alcohol consumption, for example the number of alcohol units consumed per week. No significant difference was observed in progression to BD between ischaemic and haemorrhagic strokes. This suggests that patients with cerebral infarctions can progress to BD, while physicians are currently more likely to refer patients with PH or SAH to ICUs as potential donors. The same observation can be made for location of ischaemic strokes: physicians are less likely to consider patients with a posterior circulation stroke as progressing to BD than those with anterior infarctions.

This retrospective study has some limitations that deserve to be mentioned and which are mainly due to the study design and the difficulties in collecting data because of the patients' impaired consciousness. Some data about initial GCS score and blood pressure was missing. Furthermore, it was not possible to collect some important information such as the exact time between patient identification and BD. Alcohol consumption could only be estimated from the family environment with lacked precision. In addition, the presence of brain stem reflexes was not observed directly, but their disappearance is almost always observed in ICU near BD and less in stroke units at the initial phase of stroke. A better definition of radiological criteria, such as differentiating between the types of herniation, may also improve the accuracy of the scores. The OPTC unit was called after a decision had been made to withhold therapy and depended on physician's opinion rather than any specific criteria. This could lead to selection bias, as some physicians consider, for instance, that patients with posterior stroke are not at high risk of presenting BD, or that the organs of elderly patients are not suitable for transplantation. All these limitations reinforce the need of a prospective study including more precise selection and evaluation criteria.

Conclusions

To the best of our knowledge, this is the first study to highlight predictive clinical and paraclinical factors of BD in patients at the acute phase of severe stroke and to establish a predictive score. Initial GCS score, stroke volume, herniation, hydrocephalus, initial high SBP and a history of alcohol abuse represent predictive factors of progression to

BD for patients in this setting. Taken together, these factors can form the basis of a simple score system to help physicians make a difficult decision: it could contribute to identify more accurately if a patient with severe stroke could be a potential organ donor, and improve selection of these cases to propose ICU management to preserve organs in patients with a high probability of progression to BD. This could facilitate the delicate discussions with family members to request permission for organ donation, as many find uncertainty about the patient's outcome unbearable. The findings of this study have to be confirmed by other prospective multicentre studies with a higher number of patients and including other clinical data like brain stem reflexes.

Authorship

LH, SR, A-ME, J-CL and LD: designed the study, collected data and drafted the manuscript. GM and SP: collected radiological data. RF: performed statistical analysis and drafted the parts of the Methods and Results sections.

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