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Rémy MARIMOT

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Mortality of severe non-traumatic intracerebral hemorrhage and subarachnoid haemorrhage in intensive care units: a multicenter prospective cohort study.

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Président : Monsieur le Professeur Antoine ROQUILLY

Directeur de thèse : Docteur Raphael CINOTTI

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TABLE DES MATIERES

LISTE DES ABREVIATIONS

ICH: intracerebral hemorrhage
IPH: intraparenchymal hematoma
SAH: subarachnoïdal hemorrhage
IVH: intraventricular hemorrhage
INSEE: institut national de la statistique et des etudes economiques
ICU: intensive car unit
BMI: body mass index
SAPS 2: simplified acute physiology score 2
GCS: glasgow coma scale
SBP: systolic blood pressure
SH: Subdural hematoma
EDH: Extradural hematoma
EVD: external ventricular drain
WFNS: world federation of the neurosurgical societies
HR: hazard ratio

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) is a relatively rare pathology, with an incidence varying from 10 to 37 per 100 000 person-years but some series report a higher incidence around 52 per 100 000 person-years in Asia [1][2][3]. It represents around 6.5 % to 19.6% of strokes in general [4]. Despite its relatively low incidence, ICH is a public health issue, considering its high mortality rate ranging from 30% to 35% at 7 days, 40% to 50% at 1 month, and 46% to 59% at 1 year [1][3][5][6], and does not seem to have decreased in the past decades [5][6]. Spontaneous ICH is a term that includes different kinds of haemorrhages, such as intraparenchymal hematoma (IPH), subarachnoid haemorrhage (SAH), and intraventricular haemorrhage (IVH), with their own characteristics and treatments.

Patients with IPH are often older (peak incidence around 65-85 year old [1]), and thus are more likely to present comorbidities, especially hypertension, diabetes, and chronic kidney failure, compared to other types such as SAH [7][8]. SAH has an incidence of 9.1 per 100 000 person-years [9], and a mortality rate around 43% [10]. Patients with SAH are younger than other stroke patients (around 50-60 year old) [9], and mostly women (60-70%) [10]. Thus, patients with SAH usually have fewer comorbidities, with the exception of hypertension, smoking, and alcohol intake [11][12].

According to the Institut National de la Statistique et des Etudes Economiques (INSEE), the French national institute in charge of the demographic monitoring, the aging of the French population (and of the European population) is evolving quickly, and accelerating since 2011: people over 60 year olds now represent 26.6% of the general population, versus 20.4% in 2000. Projections predict a particularly strong progression for people over the age of 75 in years to come until 2070 (www.insee.fr). In addition, aging is accompanied by an increased risk of developing comorbidities [13][14], with an incidence rate of multimorbidity (presence of two ore more chronic morbidities) reaching 65% in patients over 65 years old in the Barnett et al. study [13] based on an European population (Scotland). On the other hand, all pre-cited epidemiological studies about IPH

and SAH [1-12] are based on cohorts dating back to before 2010. Moreover, among these cohort studies, only 3 are based on the French population, from the Stroke Registry of Dijon [15][16][17].

In this context, our study aimed to compare mortality between SAH and IPH in a modern multicenter prospective cohort in France. Then, we sought to describe epidemiological difference between SAH patients and IPH patients in this modern cohort, determine day-90 mortality, and potential predictors of increased or decreased mortality.

METHODS

1. Population

All data were extracted from the French multicentre cohort ATLANREA (NCT02426255, www.atlanrea.org), that includes patients admitted in intensive care units (ICU) in the western part of France (Angers, Brest, Nantes, Poitiers, Rennes). This is a prospective cohort which started in 2013. The patient follow-up goes from the time of admission in ICU to discharge or death during their stay in ICU. An information letter was delivered to the patient after oral explanation.

Patients were eligible if they met the following criteria: hospitalization in ICU for 48 hours or more, age superior to 15-year old, non-traumatic acute brain haemorrhage requiring invasive mechanical ventilation for more than 24h hours. For the purpose of this study, only patient admitted for a non-traumatic brain haemorrhage were included, specifically patients admitted for IPH or SAH. Exclusion criteria were death within less than 24 hours post-admission, initial resuscitation for organ donation, and the refusal of the patient or his relatives to participate.

2. Data available

The recorded baseline data were age, sex, body mass index (BMI), the simplified acute physiology score 2 (SAPS 2) and the Glasgow Coma Scale (GCS) in the first 24 hours following ICU admission, history of chronic heart failure, renal insufficiency, chronic respiratory disease, diabetes, cancer, alcoholism and smoking. Baseline clinical severity data were GCS ≥9, mydriasis, Systolic blood pressure (SBP) </= 90 mmHg before admission, cardiac arrest before admission, PaO2/FiO2 ≥ 275, and intracranial pressure (mmHg). Baseline biological data were haemoglobin, leukocytes count, platelet count, prothrombin time, fibrinogen, lactate, plasma bicarbonates and pH, PaO2, FiO2, creatinine, blood glucose, blood calcium, blood urea. Specific neurological treatments of non-traumatic ICH were collected: surgical subdural hematoma (SH) or extradural hematoma

(EDH) evacuation, surgical intraparenchymal hematoma (IPH) evacuation, external ventricular drain (EVD) placement, decompressive craniectomy, osmotherapy and barbiturates use. Specific SAH treatments such as aneurysm embolization weren't included in this study, since no comparison is possible with other types of ICH.

3. Outcomes

The primary outcome was to compare mortality at 90 days between IPH and SAH, and the secondary outcomes were to determine epidemiological difference between groups, and factors associated with mortality for the whole study population.

4. Statistical analysis

Patients' baseline characteristics were compared between the IPH group and the SAH group using the Chi2 test for categorical variables and the Student t-test for continuous variables. Patient's survival was defined by the time extension between the admission and death during his stay in ICU. Patients alive at ICU discharge were censored at the date of discharge. Follow-up time was censored, 90 days post-admission in ICU for all analysis.

Concerning the primary outcome, an univariate analysis was performed to identify potential adjustment variables. Then, a multivariate and cause-specific Cox regression analysis was performed using the identified adjustment variables to compare SAH and IPH, with mortality at day-90 as dependent variable, to account for potential confounding factors. Concerning the secondary outcomes, epidemiological differences were analysed from baseline characteristics comparison, and potential predictors of mortality were identified among the adjustment variables from the multivariate analysis who showed significant association with mortality.

Cumulative incidence curves were built using the Aalen-Johansen estimator, and compared using the Gray test. Log-linearity hypothesis was verified in univariate if the Bayesian information criterion wasn't diminished by the use of a natural splines transformation compared to the covariable accounted with its usual scale. The proportional hazard assumption was checked graphically by representing the curve log(-log(survival function)) according to the two groups of interest, by studying the Schoenfeld residuals for the final model. The model was stratified on the centre. The significance level was set at 0.05. All statistical analysis were made using the Plug-Stat® software (www.labcom-risca.com) based on the R software.

RESULTS

1. Patients' characteristics

During the study period from march 1st 2013, to January 15th 2021, 1001 patients met the inclusion criteria. Eighteen patients were excluded for missing data on the primary outcome, and 983 patients were finally included in the analysis. Figure 1 presents the study's flowchart.

561 (57.1%) patients had a SAH and 422 (42.9%) had IPH. Patient in the IPH group were more frequently males (239 (57.3%) VS 214 (38.1%), p <0.0001), were older (59 (±13) years VS 56 (±12) years, p=0.0003), and had more comorbidities: chronic heart failure (15 (3.7%) VS 4 (0.7%), p= 0.001), diabetes (40 (9.7%) VS 19 (3.4 %), p<0.0001), chronic alcohol intake (85(22 %) VS 65 (12.3%), p=0.0001) with the exception of smoking which was more common in the SAH group (90 (24.7%) VS 191 (37.5%), p=0.0001). The GCS was not statistically different between the 2 groups (GCS ≥ 9 for 88 patients (21.2%) in the IPH group VS 139 (24.9%) in the SAH group, p=0.2). Regarding therapeutic interventions, EVD placement was more frequent in the SAH group (402 (71.9 %) VS 188 (44.7%), p <0.0001), and surgical intra-cranial hematoma evacuation was more frequent in patients with IPH (124 (29.5%) VS 78 (14%), p-value <0.0001). There was no significant difference regarding other therapeutics interventions, such as osmotherapy (108 (25.7%) in IPH VS 151 (27.3%) in SAH, p=0.6), barbiturates use (32 (7.6%) VS 57 (10.3%), p=0.1), or surgical SH/EDH evacuation (30 (7.1%) VS 27 (4.8%), p=0.1). Baseline characteristics of the 983 patients are presented in Table 1.

2. Univariate analysis about mortality

During follow-up, 315 patients died, with 164 (29.2%) patients in the SAH group and 151 (35.8%) in the IPH group, representing an overall day-90 mortality rate of 32% in the overall study population. Among the 40 variables analysed, 7 were identified as adjustment variables for the multivariate analysis: age (HR=1.01, 95% CI [1.01;1.02], p=0.002), GCS ≥ 9 (HR=0.54, 95% CI [0.40;0.75], p=0.0002), mydriasis (HR=2.47, 95%CI [1.95;3.13], p<0.0001), barbiturates on admission (HR=2.54, 95%CI [1.88;3.44], p<0.0001, osmotherapy on admission (HR=1.80, 95%CI [1.44;2.26], p<0.0001), EVD placement before admission (HR=0.62, 95% CI [0.50;0.78], p<0.0001), and blood glucose (HR=1.05, 95%CI [1.01;1.10], p=0.02). The univariate analysis is displayed in Table S1 in the supplemental data. In univariate analysis, the cause-specific hazard ratio (HR) between the SAH group and the IPH group regarding mortality was 0.73 (95% CI [0.59;0.91], p=0.006). Figure 2 shows the cumulative mortality incidence curves, according to the Aalen-Johansen estimator.

3. Cox regression Model

The Cox regression model was built to compare IPH and SAH using mortality at day-90, adjusted on age, GCS ≥ 9, mydriasis, barbiturates on admission, osmotherapy on admission, EVD placement and blood glucose. There was no significant difference regarding mortality between SAH and IPH (HR=0.93, 95% CI [0.71;1.21], p value = 0.6) in the multivariate analysis.

Five of the seven variables identified in the univariate analysis showed statistically significant association with mortality: barbiturate use (HR=1.76, 95% CI [1.22;2.54], p=0.002), mydriasis (HR=2.08, 95%CI [1.57;2.74], p<0.0001), and age (HR=1.02, 95%CI [1.01;1.03], p=0.0007) were associated with an increased mortality risk. GCS ≥ 9 (HR=0.66, 95%CI [0.46;0.96], p=0.03) and EVD placement (HR=0.62, 95%CI [0.48;0.81], p=0.0004) were associated with a decreased risk of mortality. The results of the multivariate cause-specific Cox regression are shown in table 3.

Validation tests of the proportional hazard assumption is presented in the supplemental section. The proportional hazard assumption was violated in 3 variables: EVD placement before admission, barbiturates on admission, and mydriasis.

DISCUSSION

In our multicentre prospective cohort, we found no difference in mortality between SAH and IPH after adjustment, with a day-90 mortality rate of 32%. IPH patients were older, more frequently male, and more likely to have comorbidities, such as chronic heart failure or diabetes.

In the literature about ICH, patients with IPH are older, and then more likely to have comorbidities, as spontaneous IPH is in most cases linked to hypertension or cerebral amyloid angiopathy [7][8][18]. IPH mortality rate of 35.8% in our study is slightly lower than what has been reported before [1][3][5][6]. In the pre-existing literature, patients with SAH are younger and with less comorbidities than IPH patients. It principally concerns middle age (50-60 year old) women, with hypertension, smoking and alcohol intake being the principal risks factors [9][11][12]. In our study we found a SAH mortality rate of 29.2%, which is in the lower range of the current literature. Mortality of SAH was around 40% in the Lovelock et al. study [10]. A recent retrospective cross-sectional Australian study found a mortality at 30 days of 27% [19].

The most recent cohorts regarding IPH show that these patients are currently getting even older: a German cohort concerning ICH patients from January 2007 to December 2009 found a mean age of 72±13 years, with a proportion of 34% of patients being 80 years old or older, and estimated this proportion to be 2.5-fold higher by the year 2050 [20]. Another epidemiological study from Netherland [21] focusing on time trends in incidence and case fatality in ICH found a decreased incidence in patients under 75 years old, which remained stable for those above 75 years old, meaning an increasing proportion of older patients. This study also showed that mortality declined in patients under 75 years old (from 40 to 28% in men and from 36 to 27% in women 55-74 years old), remaining stable for older patients. Concerning SAH, a retrospective observational Australian study that focuses on incidence and case fatality from 2008 to 2018 in patients with aneurysmal SAH from the National Hospital Morbidity Database [19] showed that patients aged 75 years or older had the greater SAH incidence. Nieuwkamp et al. [22] in their meta-

analysis including patients from 1960 to 2007 (patients from developed countries including Europe) already showed an aging tendency in patients with SAH: between 1973 and 2002, the mean age increased from 52 to 62 years old. This study also showed a decrease in SAH mortality of 0.8% per year, which is consistent with Lovelock et al., and due to improvement in SAH management [10]. Consistently, our recent cohort in western Europe suggests that mortality in patients with non-traumatic intra-cerebral haemorrhage is slightly lower than data reported in the previous decades. Even considering these more recent cohorts, all the pre-cited epidemiological studies were published before 2010: despite a thorough research in the literature, we found no new IPH or SAH cohort studies from after this date. As stated before according to the INSEE reports, we know that the aging of the population has been accelerating since 2010, but modern epidemiological data of SAH and IPH patients are lacking. The aging of the general population has probably led to an increased proportion of eldery SAH patients with comorbidities. In fact, SAH and IPH are still regarded as two very different populations, in spite of being part of the same stroke group, and we found no study in the literature that was designed to directly compare these two populations. In this context, our modern cohort appears important in the evaluation of the epidemiological specificities of SAH and IPH.

The results of our modern multicentric cohort suggest that mortality is not different between these 2 entities. IPH patients were still older and with more comorbidities, but the mean age difference with SAH patients appeared clinically poorly relevant. Still, prognostication in ICH often tends to be overly pessimistic: the ICH score and its updates showed good discrimination concerning mortality [23][24][25][26][27][28], but those models were developed not taking into account early care limitations, and thus overestimate poor outcome. This could possibly lead physicians to be less likely to perform interventions in some patients and thus could lead to self-fulfilling prophecies [29][30]. Becker et al. [31] found a proportion of 76.7% of withdrawal of care when considering cause of death in their study including IPH patients. Withdrawal of support

occurred in the first 48 hours, was less likely to occur in patients undergoing surgery, and age was associated with lack of surgical intervention. Our study advocates that ICH patients should be equally assessed during early care, given the ageing of the general population, regardless of the type of haemorrhage. Thus, a multidisciplinary evaluation should be performed in order to evaluate the relevance of the therapeutic project, in the most severe forms.

The mortality predictors we identified were age, GCS, mydriasis, and barbiturate use. Those results confirm what has already been reported in previous studies. Age [3][5][6], and especially GCS [3][5][6][32][33] are well-established independent predictive factors in mortality in ICH, and they are some of the main items in the pre-cited clinical predictive mortality scores [23][24][25]. Regarding SAH, the most important predictive factors of mortality are the World Federation of the Neurosurgical Societies (WFNS) score, the aneurysm's size (when present), age, or the Hunt and Hess grade [34]. This significant association found with the GCS, mydriasis and barbiturate use seem to emphasize that the main ICH mortality predictors are mostly reflecting the initial neurological severity of ICH, and the major role of intracranial pressure, which pleads for an early aggressive control.

EVD placement showed a reduction of mortality. In the literature, the role of surgery is debated, two large randomized-controlled trials (STICH I [35] and STICH II [36]) failed to prove superiority compared to optimal medical treatment (with the limitation of a high cross-over rate between the medical and the surgical arm), and guidelines couldn't formulate strong recommendations [37][38]. However, a meta-analysis [39] and a prospective cohort study [40] suggest that surgery could be associated with reduced mortality, especially when an IVH is present [40]. In addition, mini-invasive neurosurgery is now developing [41][42][43]. On the other hand, EVD placement has already been reported as an independent predictive factor of reduced mortality [44], particularly in most severe patients [45]. EVD placement was more frequent in SAH patients

in our study (72 VS 44%), which could reflect a more proactive surgical tendency concerning SAH, but could only be related to anatomical considerations of ICH.

There were several limits to our study. First of all, there were missing data and we did not perform multiple imputation. Also, the proportional hazard assumption for this Cox regression was violated for 3 variables: mydriasis, barbiturates on admission, and EVD placement. This violation can indicate an inaccuracy of the statistical model used in this study concerning those 3 variables, and therefore weakens the reliability of the association found. The use of another method able to analyse time-dependent variables is possible, such as a stratified Cox proportional hazard model, or a time-dependent Cox regression analysis [46][47]. This cohort didn't include patients with early do-not-resuscitate orders (before admission in ICU or in the first 24h), which can imply an underestimation of mortality and of the impact of comorbidities, with the most fragile patients not being admitted in ICU, and the exclusion of the most severe patients for whom intensive care could seem unreasonable.

CONCLUSION

In this multicentre prospective cohort study, we found no difference in the adjusted day-90 mortality rate between IPH and SAH after adjustment. We confirmed the time trends on mortality rates reduction in spontaneous intracerebral haemorrhage. Patients with IPH were older, and had more comorbidities; GCS ≥ 9 and EVD placement were associated with a better outcome, whereas older age, mydriasis and barbiturates use on admission were associated with an increased mortality. Therefore, the initial neurological severity seems to be the main prognosis predictor. Our results could encourage physicians to reconsider the widespread vision of poor prognosis in IPH and not SAH, and support aggressive control of intracranial pressure as a priority in ICH.

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APPENDICES

Figure 1. Flowchart

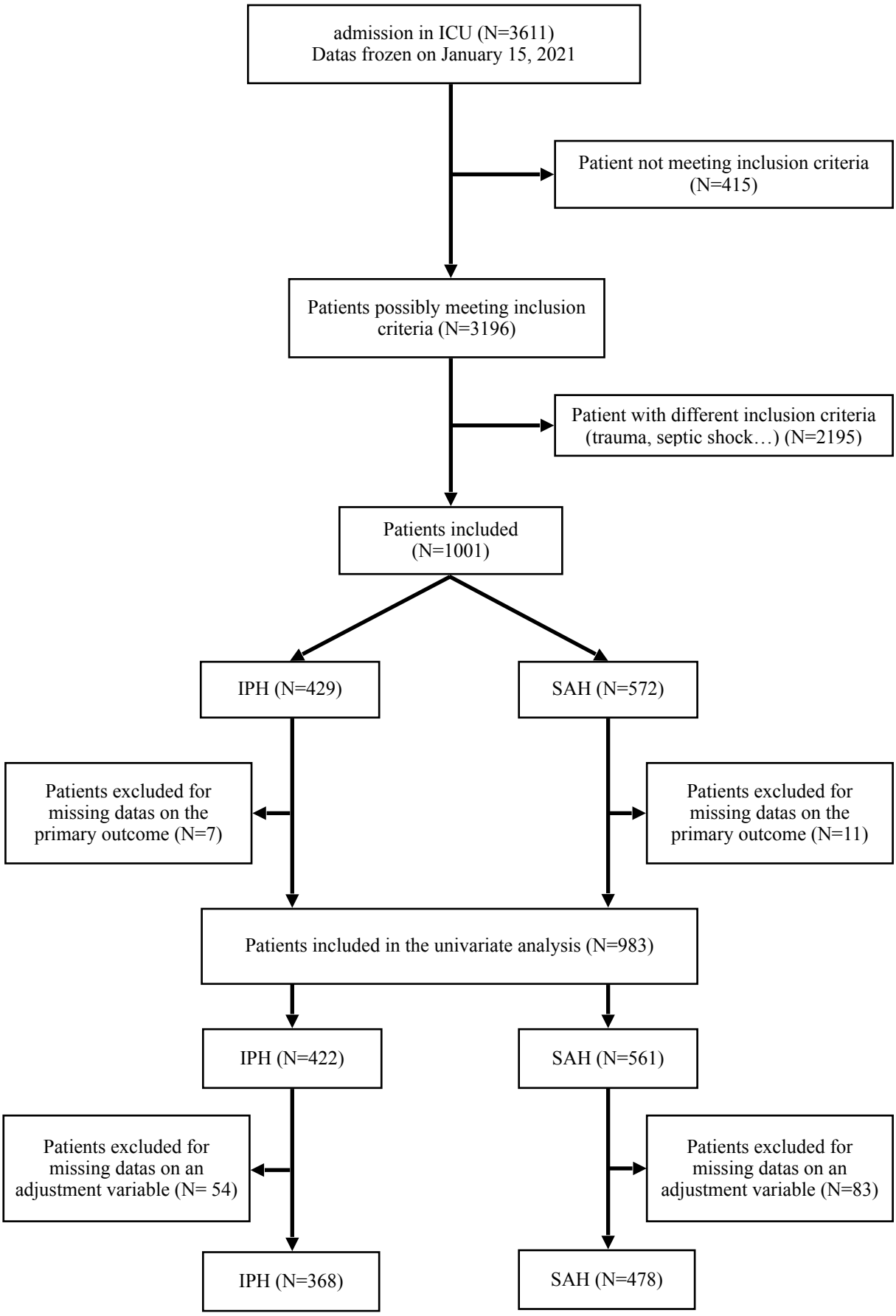


Table 1. Baseline characteristics

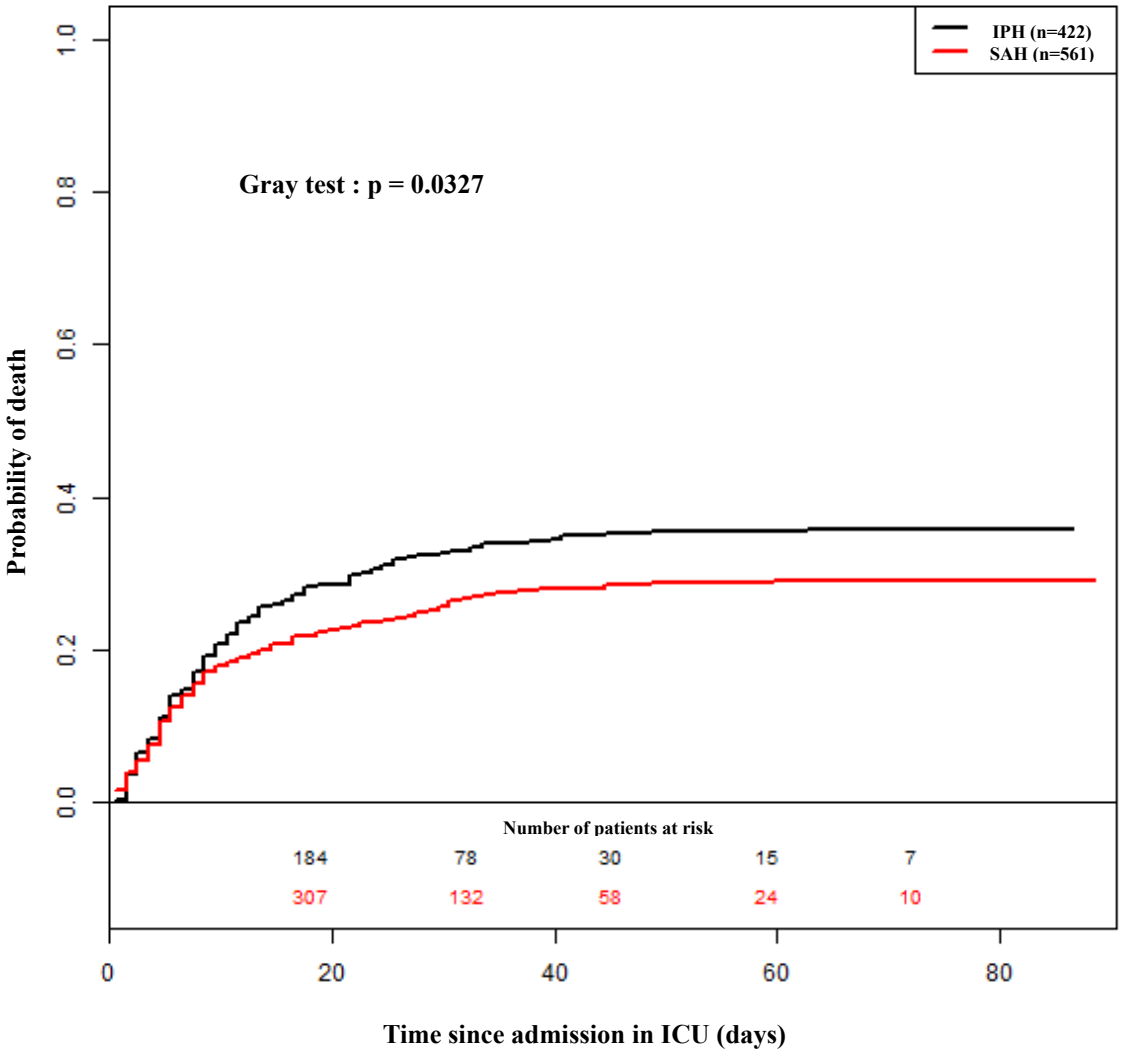
Variables	Global (n=983)			IPH (n=422)			SAH (n=561)			p-value
	NA	n	%	NA	n	%	NA	n	%	
Center	0			0			0			<0.0001
ANGERS		172	17,5		112	26.5		60	10.7	
BREST		93	9.5		38	9		55	9.8	
NANTES		249	25.3		95	22.5		154	27.5	
POITIERS		227	23.1		83	19.7		144	25.7	
RENNES		242	24.6		94	22.3		148	26.4	
Sex (male)	5	453	46.3	5	239	57.3	0	214	38.1	<0,0001
	NA	m	SD	NA	m	SD	NA	m	SD	
Age (years)	1	57.3	12.7	1	59	13	0	56.1	12.4	0.0003
BMI (kg.m2)	123	25.7	5.3	51	26.2	5.7	72	25.2	5	0.0071
Comorbidities	NA	n	%	NA	n	%	NA	n	%	
Chronic heart failure	29	19	2	17	15	3.7	12	4	0.7	0.0012
Renal insufficiency	11	20	2.1	8	9	2.2	3	11	2	0.8259
Chronic respiratory disease	30	49	5.1	17	26	6.4	13	23	4.2	0.1246
Diabetes	15	59	6.1	11	40	9.7	4	19	3.4	<0.0001
Alcoholism	67	150	16.4	35	85	22	32	65	12.3	0.0001
Cancer	13	47	4.8	9	26	6.3	4	21	3.8	0.0701
Smoking	110	281	32.2	58	90	24.7	52	191	37.5	0.0001
Immunodepression	16	25	2.6	13	13	3.2	3	12	2.2	0.3197
Clinical severity at the admission in ICU	NA	n	%	NA	n	%	NA	n	%	
GCS ≥ 9	9	227	23.3	6	88	21.2	3	139	24.9	0.1702
Mydriasis	22	199	20.7	10	89	21.6	12	110	20	0.5534
SBP </= 90 mmHg before admission	42	180	19.1	15	59	14.5	27	121	22.7	0.0016
Cardiac Arrest before admission	3	30	3.1	1	6	1.4	2	24	4.3	0.0099

Pa02/FiO2 ≥ 275	49	488	52.2	22	206	51.5	27	282	52.8	0.6919
	NA	m	SD	NA	m	SD	NA	m	SD	
Intracranial pressure (mmHg)	303	16.7	15.6	144	14	13.1	159	18.6	16.9	0.0001
SAPS II	120	47.5	11.9	45	47.5	12	75	47.4	11.9	0.9539
Therapeutic interventions	NA	n	%	NA	n	%	NA	n	%	
Barbiturates on admission	9	89	9.1	1	32	7.6	8	57	10.3	0.1465
Osmotherapy on admission	9	259	26.6	2	108	25.7	7	151	27.3	0.5896
Surgical SH/EDH evacuation before admission	4	57	5.8	2	30	7.1	2	27	4.8	0.1261
EVD placement before admission	3	590	60.2	1	188	44.7	2	402	71.9	<0.0001
Surgical IPH evacuation before admission	5	202	20.7	2	124	29.5	3	78	14	<0.0001
Decompressive craniectomy before admission	4	101	10.3	2	38	9	2	63	11.3	0.2578
Blood transfusion before admission	5	35	3.6	1	22	5.2	4	13	2.3	0.0159
Biological variables	NA	m	SD	NA	m	SD	NA	m	SD	
Hemoglobin (g/dL)	16	12.5	2	13	12.4	2	3	12.5	1.9	0.6792
Platelet count (G/L)	29	223.4	78.5	18	213.1	80	11	231	76.5	0.0005
Leukocytes count (G/L)	31	15.3	5.6	18	14.1	5.2	13	16.1	5.7	<0.0001
Prothrombin time (%)	84	83.3	16.4	46	81	18.9	38	85	14.2	0.0005
Fibrinogen (g/L)	411	3.3	1	169	3.4	1.1	242	3.3	1	0.0451
Lactate (mmol/L)	231	1.9	1.4	102	1.7	1.1	129	2	1.6	0.0100
Plasma bicarbonates (mmol/L)	37	22.2	3.3	20	22.9	3.5	17	21.7	3	<0.0001
Plasma pH	26	7.4	0.1	12	7.4	0.1	14	7.4	0.1	<0.0001
PaO2 (mmHg)	31	134.2	76.1	15	131.7	73.3	16	136	78.1	0.3851
FiO2	33	0.5	0.2	16	0.4	0.2	17	0.5	0.2	0.0270
Creatinine (µmol/L)	11	65.7	31.1	9	71.1	38	2	61.8	24.1	<0.0001

Blood glucose (mmol/L)	109	8.7	2.6	44	8.5	2.5	65	8.8	2.6	0.1730
Blood calcium (mmol/L)	151	2.1	0.2	91	2.1	0.2	60	2.1	0.2	0.0345
Blood urea (mmol/ L)	70	5.3	3.3	19	5.8	3.9	51	4.9	2.6	0.0001
Protidemia (g/L)	19	62.3	9.1	11	62.2	9.2	8	62.3	9.1	0.8728

Legend : Categorial variables were expressed using the number (n) and percentage (%), and continuous variables were expressed using the mean (m) and the standard derivation (SD). NA: not available. BMI, ICU, GCS, SAPS2, EVD: cf. abbreviations. IPH: intraparenchymal hematoma, SH: subdural hematoma, EDH: extradural hematoma, SBP: systolic blood pressure, PaO2: arterial blood oxygen partial pressure, FiO2 : inhaled oxygen fraction.

Figure 2. Compared cumulative mortality incidence curve



Compared cumulative mortality incidence curves between the IPH group (n=422) and the SAH group (n=561), according to the Aalen-Johansen calculator.

Table 2. Multivariate analysis

Variables	HR	95% CI	p-value
Age	1.02	[1.01 ; 1.03]	0.0007
GCS ≥ 9	0.66	[0.46 ; 0.96]	0.0284
Mydriasis	2.08	[1.57 ; 2.74]	<0.0001
Barbiturates on admission	1.76	[1.22 ; 2.54]	0.0024
Osmotherapy on admission	1.27	[0.95 ; 1.69]	0.1078
EVD placement before admission	0.62	[0.48 ; 0.81]	0.0004
Blood glucose	1.04	[0.99 ; 1.09]	0.0994
SAH vs. IPH	0.93	[0.71 ; 1.21]	0.5649

Cause-specific multivariate Cox model (n=846, 137 patients excluded for missing data on the evaluated variables) regarding mortality (258 death during follow-up among those 846 patients), and stratified on the centre.

Supplemental data: Table S1. univariate analysis.

Variables	Missing data	HR	95 % CI	P-value
Sex (male)	5	0.95	[0.76 ; 1.19]	0.6750
Age	1	1.01	[1.01 ; 1.02]	0.0019
BMI	123	1.00	[0.98 ; 1.02]	0.9779
Chronic heart failure	29	1.47	[0.69 ; 3.12]	0.3131
Renal insufficiency	11	0.65	[0.27 ; 1.57]	0.3363
Chronic respiratory disease	30	1.29	[0.82 ; 2.02]	0.2761
Diabetes	15	0.95	[0.61 ; 1.50]	0.8384
Alcoholism	67	0.93	[0.67 ; 1.28]	0.6386
Cancer	13	1.26	[0.76 ; 2.08]	0.3750
Smoking	110	1.02	[0.80 ; 1.31]	0.8568
Immunodepression	16	1.21	[0.65 ; 2.28]	0.5498
GCS >/= 9	9	0.54	[0.40 ; 0.75]	0.0002
Mydriasis	22	2.47	[1.95 ; 3.13]	<0.0001
SBP </= 90 mmHg before admission	42	1.08	[0.81 ; 1.43]	0.6070
Cardiac arrest before admission	3	2.43	[1.54 ; 3.82]	0.0001
PaO2/FiO2 >/= 275	49	0.92	[0.73 ; 1.15]	0.4569
Intracranial pressure	303	1.02	[1.01 ; 1.03]	<0.0001
SAPS2	120	1.03	[1.02 ; 1.04]	<0.0001
Barbiturates on admission	9	2.54	[1.88 ; 3.44]	<0.0001
Osmotherapy on admission	9	1.80	[1.44 ; 2.26]	<0.0001
Surgical SH/EDH evacuation before admission	4	1.40	[0.92 ; 2.12]	0.1169
EVD placement before admission	3	0.62	[0.50 ; 0.78]	<0.0001
Surgical IPH evacuation before admission	5	1.27	[0.98 ; 1.65]	0.0678
Decompressive craniectomy before admission	4	1.30	[0.95 ; 1.79]	0.0988
Blood transfusion before admission	5	1.01	[0.57 ; 1.79]	0.9827
Hemoglobin	16	1.01	[0.96 ; 1.07]	0.6632
Platelets count	29	1.00	[1.00 ; 1.00]	0.7759
Leukocytes count	31	1.03	[1.01 ; 1.05]	0.0025
Prothrombin time	84	1.00	[0.99 ; 1.00]	0.4257
Fibrinogen	411	1.05	[0.92 ; 1.21]	0.4721
Lactate	231	1.10	[1.03 ; 1.18]	0.0037
Plasma bicarbonates	37	0.99	[0.96 ; 1.03]	0.7235
Plasma pH	26	0.53	[0.15 ; 1.91]	0.3356

Variables	Missing data	HR	95 % CI	P-value
PaO2	31	1.00	[1.00 ; 1.00]	0.4492
FiO2	33	1.09	[0.59 ; 1.99]	0.7918
Creatinine	11	1.00	[1.00 ; 1.01]	0.0100
Blood glucose	109	1.05	[1.01 ; 1.10]	0.0206
Blood Calcium	151	0.71	0.38 ; 1.32]	0.2787
Blood urea	70	1.03	[1.01 ; 1.06]	0.0165
Protidemia	19	1.00	[0.98 ; 1.01]	0.7280

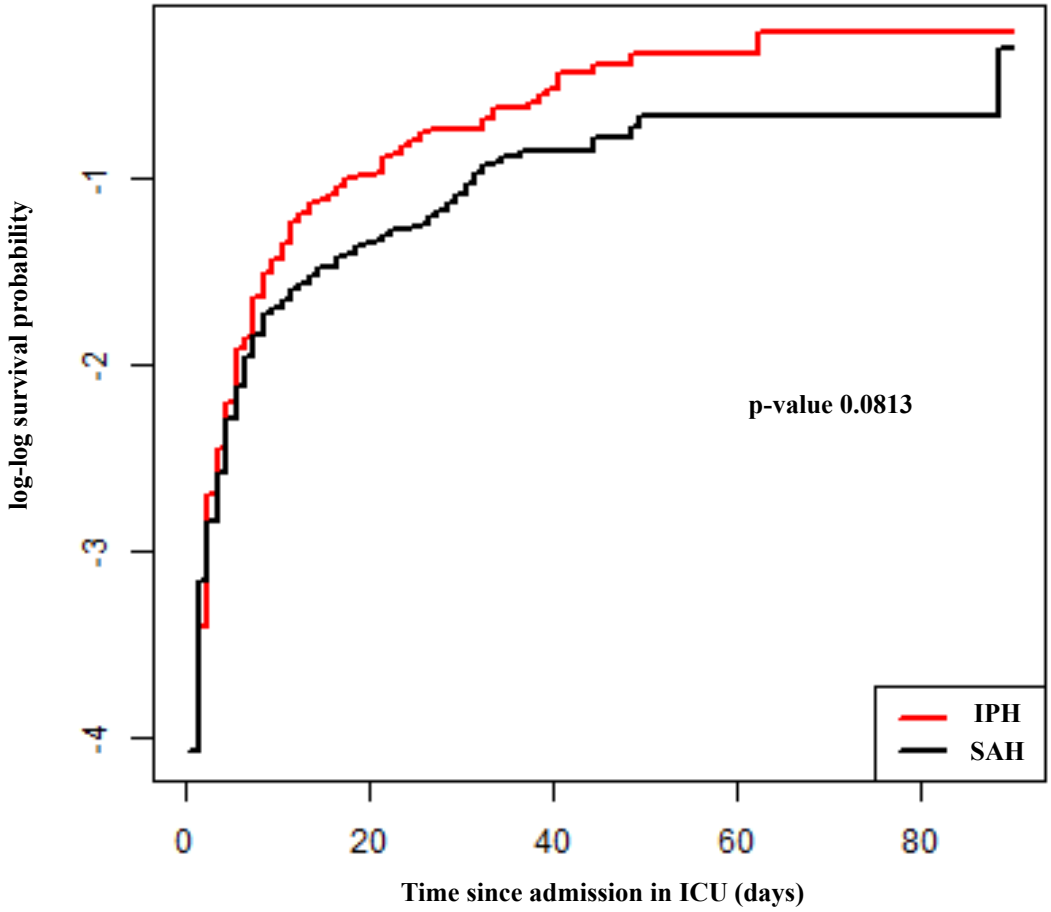
Univariate cause-specific Cox D. regression concerning death risk (n=983, 315 events (deaths), stratified on the center). HR: hazard ratio, 95% CI: 95% confidence interval. BMI, ICU, GCS, SAPS2, EVD: cf. abbreviations. SH: subdural hematoma, EDH: extradural hematoma, IPH: intraparenchymal hematoma, SBP: systolic blood pressure, PaO2: arterial blood oxygen partial pressure, FiO2 : inhaled oxygen fraction.

Supplemental data. Validation of Proportional hazard assumption (Schoenfeld residuals method)

Variables	p-value
Age	0.5064
GCS ≥9	0.4025
Mydriasis	0.0267
Barbiturates on admission	0.0422
Osmotherapy on admission	0.4779
EVD placement before admission	0.0006
Blood glucose	0.1235
SAH vs. IPH	0.0813
Global	0.0001

Results of the tests of the proportional hazard assumption of the multivariate Cox model stratified on center according to the Schoenfeld residuals method (significance level set at 0.05)

Supplemental data. Log minus log plot for the comparison between SAH and IPH



log(-log(survival function)) curve comparing IPH and SAH. The corresponding p-value according to Schoenfeld residuals is 0.0813

Appendix. the ICH score

Component	ICH Score Points
GCS score	
3-4	2
5-12	1
13-15	0
ICH volume cm^3	
≥30	1
<30	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, years	
≥80	1
<80	0
Total ICH score	0-6

The original ICH score, according to Hemphill et al., 2001 [18].

GCS score: GCS score on initial presentation (or after resuscitation); ICH volume: volume on initial CT scan; and IVH: presence of any IVH on initial CT scan.

Appendix. The World Federation of Neurosurgical Societies Scale: WFNS scale

WFNS Grade	Glasgow Coma Scale	Motor Deficit
I	15	Absent
II	14-13	Asent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or Absent

Drake, 1988, on behalf of the World Federation of Neurosurgical Societies.

Appendix. the Hunt and Hess scale

Grade	Clinical condition
0	Unruptured
I	Asymptomatic or minimal headache, nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other that cranial nerve palsy
III	Drowsiness, confusion, mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
V	Deep coma, decelerate rigidity, moribund appearance

Hunt & Hess, 1968; Ogilvy & Carter, 1998

Vu, le Président du Jury,
(tampon et signature)

Titre Prénom NOM

Vu, le Directeur de Thèse,
(tampon et signature)

Titre Prénom NOM

Vu, le Doyen de la Faculté,

Professeur Pascale JOLLIET

LAST NAME : MARIMOT FIRST NAME : Rémy

Title: Mortality of severe non-traumatic intracerebral hemorrhage and subarachnoid haemorrhage in intensive care units: a multicenter prospective cohort study.

ABSTRACT

Spontaneous intracerebral hemorrhage (ICH) is a devastating pathology with high mortality and major functional burden for survivors. Available epidemiological data date from before 2010. This multicenter prospective cohort, based on the modern Atlanrea cohort, studied 983 patients with ICH admitted in ICU, divided in two groups : subarachnoïdal aneurysmal hemorrhage group and intraparenchymal hematoma group. The aim was to compare the adjusted mortality between these two pathologies. Secondary objectives were to describe and compare SAH and IPH patient's characteristics, and determine mortality predictors in modern era. A total of 315 patient died (with 164 deaths in the SAH group and 151 deaths in the IPH group) representing a day-90 mortality rate of 32% (29.2% in SAH and 35.8% in IPH). After adjustment, there was no significant mortality difference between SAH and IPH. Patients with IPH were more likely to be male, older and with more comorbidities. Age, mydriasis and barbiturates on admission were associated with an increased mortality, and GCS ≥ 9 and EVD placement were protective factors.

KEY WORDS

Intracerebral hemorrhage, subarachnoïdal hemorrhage, intraparenchymal hematoma, epidemiology, mortality, intensive care unit

NOM : MARIMOT PRENOM : Rémy

Titre : Mortalité des hémorragies intracérébrales sévères spontanées et des hémorragies sous-arachnoïdiennes en réanimation: une étude de cohorte prospective multicentrique

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RESUME

L'hémorragie cérébrale spontanée est une pathologie gravissime avec une mortalité importante et des séquelles fonctionnelles lourdes chez les survivants. Les données épidémiologiques disponibles datent d'avant 2010. Cette étude de cohorte prospective multicentrique, à partir de la cohorte contemporaine Atlanrea, a porté sur 983 patients atteints d'hémorragie cérébrale admis en réanimation, divisés en un groupe d'hématome intraparenchymateux et un groupe d'hémorragie sous-arachnoïdienne d'origine anévrysmale. L'objectif principal était de comparer la mortalité entre ces deux pathologies après ajustement. Les objectifs secondaires étaient de décrire et comparer les caractéristiques épidémiologiques des patients selon la pathologie, et de déterminer les prédicateurs de mortalité à notre époque. Au total, 315 patients sont décédés (164 dans le groupe HSA et 151 dans le groupe HIP), soit une mortalité à J90 de 32% (29,2% pour le groupe HSA et 35,8% dans le groupe HIP). Après ajustement, il n'y avait pas de différence en termes de mortalité entre les deux groupes. Les patients du groupe HIP étaient principalement des hommes, plus vieux et plus comorbides. L'âge, la mydriase et l'utilisation de barbituriques étaient associés à une augmentation de la mortalité, et un GCS ≥ 9 et la pose d'une DVE étaient des facteurs protecteurs.

MOTS-CLES

Hémorragie cérébrale, hémorragie sous arachnoïdienne, hématome intraparenchymateux, épidémiologie, mortalité, réanimation