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Risk factors for three-month mortality of intracerebral haemorrhage in Burkina Faso

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Abstract

Background: 3-month mortality rates are becoming lower in developed countries, while they remain high in sub-Saharan Africa. The identification of mortality risk factors at 3 months, will contribute to the improvement of post ICH survival. The aim of this study was to identify 3-month risk factors for intra cerebral hemorrhage (ICH) mortality in Ouagadougou, Burkina Faso.

Patients and methods: This was a prospective cohort study, descriptive and analytic, of patients consecutively hospitalized for ICH, less than 7 days delay, diagnosed with a brain CTscan, at the University Hospital of Tingandogo, in Ouagadougou, May 2016 to May 2017. The admission data (sociodemographic, clinical and paraclinical), the intra hospital, at one month and at 3 months evolutions (complications, deaths), after the ICH, were analyzed. An univariate and multivariate analysis with logistic regression, made it possible to identify risk factors for mortality at 3 months after ICH. The data was analyzed using the Epi info 7.2 software, then STATA 15.

Results: A total of 97 patients were enrolled, with a sex ratio M / F of 3.2, an average age of 56.2 years (30 and 86 years). The mean NIHSS score was 16.3 ± 7.5 (3 and 38); coma (Glasgow ≤ 8) and severe neurological impairment (NIHSS ≥17) were present in 27 patients (27.8%) and 35 patients (36.1%), respectively. At the end of the hospitalization, then at 30 days and 90 days, post ICH, the mortality rates were respectively 32% (31 patients), 33.3% (32 patients) and 38.5% (37 patients). At the end of the multivariate analysis with logistic regression, independent risk factors for mortality at 3 months after HIC were GCS ≤8 at admission (OR = 25.31, 95% CI: 3.52-182.29 ; p = 0.001) and the NIHSS score ≥17 at admission (OR = 7.63 ; 95% CI: 1.68-34.71 ; p = 0.009).

Conclusion: 3-month mortality remains high in Sub-Saharan Africa due to poor quality of care and poor performance of health systems. Implementation of SUs, early standardization of hypertension, improved accessibility of patients to functional rehabilitation centers, and quality follow-up and rehabilitation care units will contribute to the improvement of short and medium-term survival, after ICH.

Keywords: Intracerebral hemorrhage, Mortality at 3 months, Risk factors

Introduction

Intracerebral hemorrhage (ICH) is a major global health problem. ICH is associated with the highest mortality and morbidity of all stroke subtypes, in the absence of specific therapies with proven efficacy [1]. Recent studies in developed and some emerging countries have reported a trend toward reduced mortality among HIC patients, early treated in neurovascular units (UNVs) [2]. 3-month mortality rates are becoming lower, ranging from 26.9% in Spain in 2014 [3] to 16.9% in South Korea in 2008 [4], in Finland, in 2014 [5]. These performances have been attributed to better quality of care [6-8]. The proportion of ICHs appears to be more common in Asian and black populations than Caucasians [9,10]. In Sub-Saharan Africa (SSA), despite the scarcity of studies, the same pattern of decline in post-stroke mortality has been observed [11],

but 3-month mortality rates remain the highest in the world at around 34% [12]. The low quality of care and poor performance of African health systems are the key factors [13,14]. In the context of SSA in general and Burkina Faso in particular, marked by the absence of specific therapies, Stroke Units (Sus) or pathways for stroke care, as well as a low accessibility to quality functional rehabilitation, the identification of risk factors for 3-month mortality of ICHs, could help improve the survival of these patients in the short and medium terms.

The aim of this study was therefore to identify risk factors for 3-month mortality of ICHs, in Ouagadougou, Burkina Faso, through a prospective cohort study.

Patients and Methods

It was a prospective cohort, observational, descriptive and analytical study, conducted at the Tingandogo University Hospital Center, one of four tertiary hospitals in Ouagadougou, capital of Burkina Faso. Our study took place in the Department of Neurology, during a period of 12 months, from June 1, 2016 to May 31, 2017; it concerned adult patients, > 16 years of age, of all sexes, consecutively hospitalized at the Tingandogo University Hospital, during the study period, for non-traumatic intracerebral hemorrhage (HIC), confirmed by cerebral CT, dating from at most 7 days before hospitalization, excluding traumatic intracerebral haemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis, cerebral infarction, hemorrhagic transformation of cerebral infarction and other neurological pathologies. Also were not included in the study, patients who were unable to perform a cerebral CT scan, those who died before arrival at the hospital, those for whom consent to participate in the study was not obtained and those whose stroke was more than 7 days old at admission.

For any patient, a medical file containing antecedents (vascular risk factors, comorbidities), measurement of vital constants, initial neurological and general clinical evaluation by a senior neurologist, standard ECG, cerebral CT interpreted by a radiologist, standard initial blood test, was held. The volume of the ICH was calculated radiologically by the formula A.B.C / 2, where A represents the largest diameter of the lesion in millimeters (mm), B represents the diameter (mm) perpendicular to A and C the thickness of the lesion (mm) which is calculated as follows: number of sections visualizing the lesion multiplied by the thickness of the section (mm). The topography of the HIC was classified as supratentorial (lobar, deep), infratentorial (brainstem, cerebellum) and pure intraventricular or mixed.

Complications and intercurrent clinical events were recorded as they appeared from admission through to the end of hospitalization, and then out of hospital (for patients who had survived) at 90 days post stroke. The management of stroke was done according to the recommendations of the European Stroke Organization (ESO) 2008 [15].

The standard chest x-ray was performed if there was suspicion of bronchopulmonary infection, some biological examinations for monitoring metabolic disorders, venous doppler ultrasound and thoracic CT angiography, respectively if there was suspicion of venous thrombosis of the limbs or pulmonary embolism ; thick blood, cytobacteriological examination of urine, blood cultures, respectively in case of suspected access to malaria, urinary tract infection, sepsis. Control brain CT scan was not systematic; it was performed in case of neurological deterioration or unusual headache and if the patient or his family could meet the costs of the examination. At the end of the hospitalization, patients were subdivided into surviving patients or deceased patients. When the death occurred during hospitalization, the immediate causes of death were determined in staff of senior neurologists. Each patient received a follow-up of at least 90 days, corresponding to 3 months, starting from the date of the beginning of the stroke, including a hospital phase and a post-hospital phase for the patients who survived the hospitalization. To do this, each surviving patient, when discharged from hospital, was summoned for an external clinical evaluation of neurology that was to coincide with the 30th and 90th days post stroke. This evaluation included, among other things, the clinical assessment of functional outcome according to the modified Rankin score (mRS). Prior to this review date, patients or their families were called weekly to learn about their clinical course. In the event of death during this post-hospital phase, the time and circumstances of death were obtained from the family of patients by telephone. Some patients who were unable to attend the neurological check-up at hospital were evaluated at home or by telephone.

Study variables included socio-demographic characteristics (age, gender), admission clinical data (admission delay, vascular risk factors, comorbidities, admission constants, Glasgow Coma Score (GCS) at baseline admission, National Institute of Health Stroke Scale score (NIHSS) at admission), qualitative biological data at admission (blood glucose, serum creatinine, serum sodium, serum potassium, blood count), cerebral CT data at admission (ICH topography and volume, lesions and associated neuroradiologic complications), intra-hospital evolutionary data [(length of hospital stay, vital prognosis (deceased / survivors)] and evolutionary data at 30 days and 90 days post HIC [vital prognosis (deceased / survivors)] A GCS ≤ 8 defined a coma ; a NIHSS score ≥ 17 defined a severe neurological deficit. The volume of the ICH was classified as low volume HIC e (≤ 30 cc), ICH medium volume (30-60 cc) and ICH large volume (> 60 cc).

The data entry and analysis was done using the software Epi info 7.2, then STATA 15. Student's t-test was used to compare the means and the Pearson chi² test to compare the percentages; the value of $p \leq 0.05$ was considered as a threshold of statistical significance. To determine mortality risk factors at 3 months, an uivariate analysis was first performed to find an association between the socio-demographic, clinical, biological and neuroradiological variables present at admission and the 3-month mortality. Then, a multivariate analysis with the use of the logistic regression model step by step, identified the

independent risk factors of 3-months mortality. Only variables with $p \leq 0.20$ in the univariate analysis were included in the multivariate analysis.

The consent of patients or their legal representatives, as well as the anonymity of the investigation, were guaranteed prior to recruitment. The protocol of the study was approved by the national ethics committee of Burkina Faso, then authorized by the General Direction of the University Hospital of Tingandogo.

Results

Descriptive study

During the study period, 248 patients were admitted for stroke at Tingandogo University Hospital, including 97 cases of HIC, corresponding to 39.1% of strokes. The mean age of the patients was 56.2 ± 12.1 years (range, 30 to 86 years). There was male predominance, with an M / F sex ratio of 3.2. High Blood Pressure (HBP) and alcoholism with 79 cases (81.4%) and 18 cases (18.6%), respectively, were the main vascular rik factors (VRFs). Comorbidities were found in 19 patients, ie 19.6%. The mean admission time was 17.7 ± 25.2 hours (range 1 to 96 hours), the median was 6 hours. At admission, mean BP was 172 ± 36.4 / 102 ± 19.1 mmHg (range 101 to 280/46 to 153 mmHg), the mean NIHSS score was 16.3 ± 7.5 (range 3 and 38); coma (GCS ≤ 8) and severe neurological impairment (NIHSS ≥17) were present in 27 patients (27.8%) and 35 patients (36.1%), respectively. Headache, boost of HBP and hyperthermia were present at admission in 85 patients (87.6%), 71 patients (73.2%) and 18 patients (18.6%), respectively. The mean time to perform the brain scan was 3.7 ± 4.8 hours (range 0.5 to 24 hours), the median was 2 hours.

Hyperglycemia with 35 cases (36.1%), leukocytosis with 18 cases (18.6%) and anemia with 14 cases (14.4%) were the main laboratory abnormalities observed at admission. The supratentorial topography ICH with 90 cases (92.8%) were dominated by deep ICHs, capsulothalamic with 30 cases (30.9%), capsulolenticular with 23 cases (23.7%) and polylobal with 12 cases (12, 4%). ICHs of infra tentorial topography with 7 cases (7.2%) were dominated by cerebellar HICs with 6 cases (6.2%). The mean initial volume of the ICH was 34.9 ± 18.1 cc (5 and 91cc). The volume of HIC was ≥ 60cc in 18 patients or 18.6%. Cerebral edema with 40 cases (41.2%), mass effect with 36 cases (37.1%) and ventricular flood with 32 cases (33.3%), were the main signs of neuroradiological severity present upon admission. A cerebral microangiopathy due to chronic hypertension with 72 cases (74.2%) was the main etiology; no cause was found in 14 cases (14.4%). Pulmonary infection with 39 cases (40.2%), neurological deterioration with 32 cases (32.6%) and cardiac decompensation with 15 cases (15.5%), were the most common intra-hospital complications. The socio-demographic, clinical and biological characteristics, the neuroradiological characteristics, as well as the etiological characteristics and intra-hospital complications encountered in patients, are presented in **Tables 1-3**.

Table 1. *Caractéristiques socio-démographiques, cliniques et biologiques rencontrées chez les 97 patients lors de l'admission.*

Vascular risk factors		
HBP	79	81.4
Alcohol	18	18.6
Smoking	10	0.3
Diabetes	6	6.2
Antithrombotic treatment	2	2.1
Comorbidities	19	19.6
Clinical features at admission		
GCS [9-14]	32	33
GCS ≤ 8 (coma)	27	27.8
Headaches at admission	85	87.6
Boost HBP at admission	71	73.2
Fever at admission	18	18.6
Neurological deficit on admission		
· Light to moderate (NISS ≤16)	62	63.9
· Severe (NIHSS ≥17)	35	36.1
Epileptic seizures at admission	5	5.2
Biological abnomalities at admission		
Hyperglycemia	35	36.1
LeuKocytosIS	18	18.6
Anemia	14	14.4
Hyponatremia	10	10.3
Elevated créatinine	10	10.3
Hypoprotidemia	9	9.3
Hypernatremia	8	8.2
Hypokaliemia	7	7.2

Table 2. *Neuroradiological characteristics in 97 patients on admission.*

Topography of ICH		
Deep supratentorial	64	66
· Capsular ad thalamic	30	30.9
· Capsuolar and lenticular	23	23.7
· Extensive bleeding	11	11.4
Supratentorial lobar	24	24.7
Pur intraventricular	2	2.1
Cerebellar	6	6.2
Brainstem	1	1.1
ICH volume		
≤ 30 cc	52	53.6
30-60 cc	27	27.8
≥ 60 cc	18	18.6
Severe neuroradiological signs on admission		
Cerebral edema	40	41.2
Mass effect	36	37.1
Ventricular flood	32	33.3
Cerebral herniation	25	25.8
Acute hydrocephalus	14	14.4
Other neuroradiological abnormalities		
Leukoaraiosis	26	26.8
Sequelae lesions	13	13.4

The mean lengh hospital was 11.7 ± 7.6 days (range 1 to 49 days), the median was 10 days. Of the 97 patients, 31 patients died (mRS = 6) during hospitalization, corresponding to an intra-hospital mortality rate of 32%, with a mean time of death of 7.1 ± 4.2 days (range 1 and 16 days). Of the 66 patients discharged alive (68.0%), 24 (36.4%) were independent or autonomous

Table 3. *Aetiological features and intra-hospital complications in 97 patients at admission.*

Etiologies of ICH		
Cerebral microangiopathie by chronic HBP	72	74.2
Indeterminate causes	17	17.5
Cerebral vascular malformation	3	3.1
Antithrombotic treatment	2	2.1
Brain tumor	2	2.1
Cerebral amyloid angiopathy	1	1.0
Complications and intra hospital intercurrent events		
Pulmonary infection	39	40.2
Urinary infection	12	12.4
Sepsis	1	1.0
Undernutrition	12	12.4
Extracerebral hemorrhage	3	3.1
Bedsores	6	6.2
Urinary incontinence	19	19.6
Deep vein thrombosis of limb	3	3.1
Cardiac compensations	15	15.5
· Heart rhythm disorders	8	8.2
· Heart failure	7	7.2
Respiratory distress	3	3.1
Neurogical deterioration	32	32.6
Epileptic seizures	14	14.4

(mRS = 0-2) and 42 patients (63.6%) were dependent (mRS = 3-5). At 30 days post stroke, 1 additional patient died, bringing the number of deceased patients to 32, giving a 30-day mortality rate of 33.3%. Of the 65 patients surviving at 30 days, 29 patients (45.3%) were independent or autonomous (mRS = 0-2) and 35 patients (54.7%) were dependent (mRS = 3-5). Only one patient was lost sight of.

The immediate causes of death were represented by direct complications of HIC in 29 cases (90.6%) and pulmonary infections in 3 cases (9.4%). At 90 days or 3 months post-stroke, 5 additional patients died, bringing the number of deceased patients to 37, corresponding to a cumulative mortality rate at 3 months post ICH of 38.5%. Of the 59 surviving patients, 39 or 61.10% were autonomous or independent and 20 or 33.90% of patients were dependent. Immediate causes of death were represented by pulmonary infection 2 cases, respiratory distress complicating pulmonary embolism 2 cases and unknown 1 case.

Analytical study

In univariate analysis, the variables significantly associated with the 3-month mortality of the HICs, present on admission, were: NIHSS score ≥17 ($p < 0.001$), GCS ≤ 8 ($p < 0.001$), initial hematoma volume ≥60 ($p < 0.001$), diffuse cerebral edema ($p < 0.001$), cerebral herniation ($p < 0.001$), mass effect ($p < 0.001$), initial hydrocephalus ($p < 0.001$), ventricular flood ($p < 0.001$), renal failure ($p = 0.0182$), hypernatremia ($p = 0.0182$). **Table 4** presents the results of the univariate analysis. At the end of the multivariate analysis according to the step-by-step logistic regression model, the independent risk factors of mortality at 3 months after HIC were: GCS ≤8 at admission (OR = 25.31, 95% CI: 3.52-182.29, $p = 0.001$); NIHSS score ≥17 at admission (OR = 7.63, 95% CI: 1.68-34.71, $p = 0.009$).

Discussion

There is little data on 3-month mortality of ICHs in SSA. We can nevertheless mention the Kaduka L et al studies in Kenya [12], which reported high rates at 34.5%, close to the high 3-month mortality rate of 38.5% reported in our study. Data on the 3-month mortality of stroke in general (ischemic and hemorrhagic) in this region of the world, find rates equally high: 31.7% in Cameroon [16], 52% in The Gambia [17].

The low quality of care and poor performance of African health systems, including the lack of medical equipment and qualified human resources, the absence of SUs and organized stroke pathways, the low accessibility and / or availability of functional rehabilitation centers and follow-up care and rehabilitation units, are the main factors [13,14,18].

In developed countries and some emerging countries, there has been a general trend towards improving the short-term survival of ICHs in the past decade, resulting in ever-decreasing 3-month mortality rates: 26.9 % in Spain [3], 25% in Denmark [19], 23.9% in China [20], 19% in USA [21], 17% in Taiwan [22] , 16.9%, respectively, in South Korea [4], in Finland [5]. A high mortality rate of 34% in 2006 was still reported in Israel [23] and a very low rate of 11.7% was reported in China in 2016, but only for hypertensive HIC [24]. These favorable developments observed in the developed countries and some emerging countries are certainly due to a better quality of care, resulting from the structuring of the stroke pathways, the development of SUs and the evolution of medical techniques, particularly the timely transport of medical devices, evidence-based medical interventions such as the early and rapid decline in HBP thrust at the early phase of ICH [6,7,8]. In addition, the improvement of tertiary prevention, with the development of functional rehabilitation centers and after-care and rehabilitation services, and the improvement of therapies aimed at reducing the risk of recurrent stroke and death, have helped reduce mortality [25].

The initial severity of stroke, often measured by the NIHSS score, has been shown to be a strong predictor of mortality and functional outcome at 3 months after stroke in many studies [5, 22]. This observation has also been demonstrated in our study. In addition to the NIHSS score, the GCS also predicts short-term mortality in ICH patients. Thus, impaired alertness on admission has been identified as one of the most powerful predictive factors for ICH death in several studies [22,26,27,28-31], as in our study, where coma at admission increased the risk of death at 3 months by a factor of 25. The initial severity of neurological deficit and impaired alertness on admission are a direct reflection of the extent and severity of the brain injury. The resulting neurological complications, mainly intracranial hypertension and cerebral involvement, are the immediate causes of early post-ICH deaths [4]. During the short or medium terms, patients who have survived the early phase, especially those with severe

Table 4. Results of univariate analysis (risk factors of mortality at 3 months post ICH.

Variables	survivivants	Deceased	OR [95%IC]	p
Age > 50 years	46(67.65)	22(32.35)	0.42 [0.17-1.02]	0.0663
Male gender	46(62.16)	28(37.84)	0.88 [0.33-2.32]	0.81
Comorbidities	11(57.89)	8(42.11)	1.20 [0.43-3.34]	0.7947
GCS ≤ 8 (coma) at admission	2(7,69)	24(92.31)	52.62 [11.02- 251.20]	<0.001
NIHSS ≥ 17 at admission	6(17.65)	28(82.35)	27.48 [8.88-85.06]	<0.001
Epileptic seizures at admission	0 (00)	4(100.00)	-	0.500
HBP at admission	54(62.79)	32(37.21)	0.59 [0.16-2.21]	0.5012
Hyperglycemia admission	17(45.95)	20(54.05)	1.49 [0.58-3.80]	0.4791
Hypoprotidemia at admission	6(50.00)	6(50.00)	1.03 [0.30-3.58]	0.9750
Elevated creatinine at admission	3(21.43)	11(78.57)	5.04 [1.27-20.05]	0.0182
Leukocytosys on admission	6(42.86)	8(57.14)	1.48 [0.46-4.48]	0.5628
Fever on admission	6(33.33)	12(66.67)	2.00 [0.87-2.98]	0.1935
Hyponatremia	11(73.33)	4(26.67)	0.28 [0.080-0.99]	0.0805
Hypernatremia	3(21.43)	11(78.57)	5.04 [1.27-20.05]	0.0182
Hypokaliemia	10(58.82)	7(41.18)	0.63 [0.21-1.89]	0.5781
Anémie	3(37.50)	5(62.50)	1,83 [0.40-8.34]	0.4782
Infratentorial ICH	2(28.53)	5(71.43)	4.68 [0.86- 25.52]	0.100
ICH volume > 30cc	22(43.14)	29(56.86)	3.19 [1.29-7.56]	<0.001
Diffuse cerebral edema	12(30.77)	27(69.23)	12.83 [4.93-33.36]	<0.001
Mass effect	9(25.71)	26(74.29)	13.13 [4.83-35.71]	<0.001
Cerebral herniation	1(4.00)	24(96.00)	97.08 [13.26-664.74]	<0.001
Ventricular flood	7(22.58)	24(77.42)	13.45 [4.76-38.02]	<0.001
Early acute hydrocephalus	1(7.14)	13(92.86)	31.42 [3.90-253.72]	<0.001

neurological deficit and / or persistent impairment of alertness, remain at risk of developing several types of potentially fatal medical complications, including pulmonary infections, pulmonary embolism, bedsores, [4,32,33]. Similar observations were make in our study. Thus treatments aimed at reducing the clinical severity and volume expansion of ICH, including hospitalization in SU, early control of homeostatic parameters such as hypertension, prevention and optimal management of post-stroke complications, better patient access to functional rehabilitation and quality follow-up and rehabilitation services, will contribute significantly to the reduction of early mortality in the short and medium terms, post-stroke.

Other independent predictors of 3-month mortality include subtentorial localization of ICH, hydrocephalus, cerebral involvement, multiple hemorrhagic localizations, intraventricular extension of hemorrhage, higher hematoma volume at 30 cc, are also described [28,34,35]. These factors, however, were not identified in our study. In a study conducted in China [24], advanced age was identified as a predictor of 3-month mortality of hypertensive HICs. This factor was not identified in our study, as 52.5% of patients aged ≤ 50 years died at 3 months, compared to 32.2% of those aged> 50 years (p = 0.066).

Limitations of our study

The small size of our study population may have contributed to decreasing the statistical power of our results.

The hospitable character of our study may have contributed to a selection bias for the most serious patients.

We included in our study some patients transferred from 2nd level hospitals, but patients who died before transfer to our hospital were not included.

We also included in our study hospitalized patients up to 7 days after the installation of the HIC and the delays of realization of the cerebral CT were spread out, which induces a certain clinical and radiological heterogeneity within the patients. Finally, our study excluded patients who could not perform cerebral CT because of lack of financial means.

Conclusion

The 3-month mortality of ICHs in SSA and Burkina Faso remains one of the highest in the world, due to poor-performance and low quality of health care systems. The initial impairment of alertness and the initial severity of ICH are the leading risk factors for death at 3 months. Implementation of SUs, monitoring of homeostatic parameters, early standardization of HBP, prevention of complications, better accessibility of patients to functional rehabilitation centers and quality follow-up and rehabilitation units, contribute to improved survival in the short and medium term after HIC.

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