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Etiologies and factors associated with mortality in patients with non-traumatic coma in a tertiary hospital in Bukavu, eastern Democratic Republic of the Congo

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ABSTRACT

Non-traumatic coma (NTC) is a common medical condition often associated with poor outcomes. Identifying underlying causes is crucial for effective management and prognostication, particularly in resource-poor settings. This study aimed to identify the most common causes and prognostic factors of NTC in a tertiary hospital in Bukavu, in the eastern Democratic Republic of the Congo (DRC), using the Glasgow Coma Scale (GCS) as well as other simple and affordable clinical and paraclinical tools. This retrospective observational study included 219 consecutive patients admitted to the intensive care unit of the Provincial General Hospital of Bukavu between January 2016 and December 2018. Sociodemographic, clinical, and laboratory data were also collected. Bivariate and multivariate analyses were performed to identify different causes and factors associated with poor outcomes in these patients. The median age of the patients was 49 (interquartile range [IQR]: 33–61) years, and they were predominantly men (62.8%). The most common causes of NTC were stroke (25.7%), acute metabolic complications of diabetes (21.9%), and primary brain infections (meningoencephalitis, 16.0%; and cerebral malaria, 14.2%). The NTC-related in-hospital mortality rate was 35.2%. A high mortality was significantly and independently associated with a GCS<7 (adjusted odds ratio [OR]: 4.30, 95% confidence interval [CI]: 1.73–10.71), the presence of meningismus at clinical evaluation (adjusted odds ratio [aOR] 3.86, 95%CI: 1.41–10.55), oxygen saturation <90% (aOR 3.99, 95%CI: 1.71–9.28), the consumption of traditional herbal medicines prior to hospital admission (aOR 2.82, 95%CI: 1.16–6.86), and elevated serum creatinine (aOR 1.64, 95%CI: 1.17–2.29). In conclusion, clinical neurological examinations, along with simple and affordable paraclinical investigations, can provide sufficient information to determine the etiology of NTC and evaluate the prognosis of comatose patients, even in resource-poor settings. Physicians may use the GCS as a simple, reliable, and affordable tool to identify patients who require special attention and care.

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1. Introduction

Consciousness is the brain function that regulates arousal and responsiveness to external environmental stimuli. Several clinical scales have been extensively used worldwide to assess level of consciousness. The Glasgow Coma Scale (GCS), which independently evaluates three clinical markers of level of consciousness (motor responsiveness, verbal performance, and eye opening), is one of the most widely used and accepted clinical scales for both traumatic and non-traumatic altered levels of consciousness [1,2]. This scale has the advantage of being easy to use even in resource-limited contexts, as it does not require any specialized equipment; and of having a high prognostic value in patients with impaired consciousness [3].

Impaired consciousness is among the most common reasons for admission to an emergency department (ED) or intensive care unit (ICU) [4]. Impaired levels of consciousness constitute a spectrum of conditions, ranging from drowsiness or lethargy (characterized by mildly depressed alertness) to coma (characterized by a state of unarousable unresponsiveness) [5]. Coma is defined as a state of profound unresponsiveness in which the patient is unaware of external (environmental) stimuli and inner needs, and cannot be aroused in response to any stimulation [6]. Non-traumatic coma (NTC) is a very common medical condition that may represent a life-threatening emergency associated with high mortality [7,8]. Indeed, NTC represents approximately 1% of all emergency rooms admissions and is often associated with poor outcomes even in developed countries, with a mortality rate ranging from 25% to 87% [9].

Hence, NTC usually requires prompt management and etiological diagnosis to preserve brain function and the patient's life [10]. Although the recognition of coma, mainly based on the clinical evaluation of the level of consciousness, is relatively easy, the etiological differential diagnosis is challenging, especially in resource-limited countries [3]. In developed countries, several strategies (including electrophysiological recordings and brain imaging) have been used to identify the etiology of coma and predict the outcomes of comatose patients [11,12]. However, such strategies are not suitable for settings where human and material resources, such as diagnostic imaging services, are limited [3]. In low-income countries, especially in remote areas, the diagnosis and management of NTC are primarily based on proper clinical evaluation and basic biological investigations. This limits the identification of the underlying causes of coma in these countries and may predispose comatose patients to poor outcomes.

To the best of our knowledge, only one study has investigated the etiology and prognosis of NTC in adults living in the Democratic Republic of Congo (DRC). In this study, conducted in Butembo (eastern DRC), NTC accounted for 31.8% of all admissions to the ICU from January 2015 to December 2016 and was associated with a mortality rate of 36% [13]. However, the definition criteria for NTC were not provided in the corresponding report, which severely limits the interpretation of these results. Furthermore, despite improvements in diagnostic tools and recent recruitment of qualified personnel in South-Kivu (eastern DRC), few studies have investigated the causes of NTC in the region to facilitate targeted management. This study aimed to determine the most frequent etiologies of coma and to identify predictors of short-term mortality in patients admitted to a tertiary university hospital in Bukavu, South-Kivu, using clinically accessible biological and imaging parameters.

2. Methods

2.1. Study design and settings

This retrospective observational study was conducted in the ED and the ICU of the "Hôpital Provincial Général de Référence de Bukavu" (HPGRB). The HPGRB is a tertiary teaching hospital for undergraduate and postgraduate medical students and is the main healthcare facility in Bukavu. Bukavu, the capital city of the province of South-Kivu in eastern DRC, has a population of approximately one million (density: 16,600 inhabitants/km^2) [14]). This war-torn province has experienced socioeconomic and political instability since the late 1990s, impacting the well-being of its population [15–17].

2.2. Selection of participants and data collection

We used an exhaustive sampling technique, and recruited all patients aged >16 years who were consecutively admitted due to NTC to the ED or ICU of the HPGRB over a period of three years (January 2016 to December 2018). NTC was defined as a GCS score ≤8 in the absence of sedative medications [18,19] in a patient with no history of head trauma. The GCS score was evaluated by two specialist medical doctors: an emergency and critical care medicine specialist and a neurologist. The GCS score was assessed upon admission, 24 h later, 48 h later, and at discharge from the intensive care unit. The first evaluation was performed in the emergency room, and subsequent evaluations were performed in the intensive care unit. Inclusion criteria were: (i) patients of both sexes, (ii) older than 16 years, (iii) admitted to the emergency room with altered consciousness, and (iv) with a GCS score ≤8/15. The exclusion criteria were as follows: (i) head trauma, (ii) surgery, or (iii) sedative medication. We retrospectively collected data from the medical records of the patients meeting our selection criteria, using a pre-established data collection form. We retrieved data from 220 patients, of whom one patient with missing information on the final outcome was excluded from the analyses, resulting in a final sample size of 219 participants.

2.3. Variables

The main outcome in this study was the vital outcome at discharge from the ICU, defined as a dichotomous variable: "improvement"

Table 1
Demographic, clinical, and biological characteristics of the studied population (n = 219).

Parameters	Frequency or Median	Percentage or IQR
Age (in years)[a]	49.0	33.0–61.0
Sex		
Female	82	37.44
Male	137	62.56
Provenance		
From another hospital	123	56.16
From a primary care health center	19	8.68
From home	77	35.16
Coma onset		
Sudden	56	25.6
Progressive	163	74.4
Time from coma onset to admission (in hours)[a]	24.0	12.0–48.0
Use of traditional medicinal plants	66	30.14
Medical history		
Arterial hypertension	74	33.79
Diabetes mellitus	48	21.92
HIV infection	13	5.99
Epilepsy	3	1.38
Major associated symptoms		
Headaches	124	56.62
Fever	97	44.29
Vomiting	83	37.90
Seizures	25	11.42
Clinical examination		
GCS score[a]	7	6–8
Temperature (°C)[a]	36.9	36.2–38.0
Heart rate (bpm)[a]	102	78–112
Respiratory rate (cpm)[a]	24	22–28
Systolic blood pressure (mmHg)[a]	120	100–190
Diastolic blood pressure (mmHg)[a]	74	60–110
Oxygen saturation (%)[a]	92	88–95
Neurological deficit		
Yes	61	27.85
No	158	72.15
Meningismus		
Yes	49	22.37
No	170	77.63
Papillary edema[b]		
Yes	46	25.41
No	135	74.59
Biological parameters		
Total blood count[b]		
White blood cell count (x1000/μL)[a]	9.5	6.2–12.7
Neutrophiles (x1000/μL)[a]	7.1	4.1–10.1
Lymphocytes (x1000/μL)[a]	1.8	1.1–2.3
Neutrophiles to lymphocytes ratio[a]	3.85	2.41–6.52
Platelets count (x1000/μL)[a]	224	145–327
Hemoglobin (g/dL)[a]	14.1	11.3–15.6
Anemia		
Yes	68	31.6
No	147	68.4
Kidney function[b]		
Blood urea nitrogen (mg/dL)[a]	37.0	27.0–72.5
Serum creatinine (mg/dL)[a]	1.25	1.10–1.95
Impaired renal function		
Yes	92	42.8
No	123	57.2
Serum electrolytes[b]		
Potassium (mmol/L)[a]	4.45	4.11–5.08
Natrium (mmol/L)[a]	139.0	135.7–143.6
Chloride (mmol/L)[a]	105.4	100.3–110.0
Calcium (mmol/L)[a]	2.11	2.01–2.20

[a] Data were presented as medians and interquartile ranges. All other parameters are expressed as frequency with corresponding percentage.

[b] For the variable "Papillary edema", the total number of observations was 181 since fondus oculus had not been performed in 38 patients. For total blood count parameters, n = 217; for kidney function and serum electrolytes, n = 215 due to missing values; for all other variables, n = 219.

(for patients who showed an improvement in their GCS score, i.e. reached a GCS score >8 and were discharged alive from the ICU) or "death" (for patients who died during their stay at the ICU), in accordance with the information retrieved from the medical records.

We collected sociodemographic characteristics (age and sex), timing and mode of coma onset (the onset was considered sudden if the coma occurred within a few seconds or minutes, or progressive if it occurred within hours or days), medical history (use of traditional medicinal plants prior to hospital admission; history of epilepsy, diabetes mellitus, or arterial hypertension; and infection by the human immunodeficiency virus [HIV]), clinical/neurological signs at admission (vital signs, GCS score, oxygen saturation [SaO2] measured at ambient air using a pulse oximeter, presence or absence of a focal neurological deficit, presence or absence of meningismus, findings of fundus oculus (especially the presence of a papillary edema), laboratory findings at hospital admission (complete blood count parameters, blood urea nitrogen [BUN], serum creatinine, serum electrolytes, and cerebrospinal fluid analyses when available), brain imaging if performed, final diagnosis recorded in the medical files, and vital outcome at discharge from the ICU (improvement or death).

Based on clinical, biological, and brain imaging information, the causes/etiologies of coma are divided into structural or primary brain disorders (stroke, meningoencephalitis, or brain tumors, among others) and non-structural or systemic disorders (medical conditions that secondarily cause diffuse brain dysfunction such as metabolic disturbances, septic shock, or hypertensive hypertension, among others) [20].

2.4. Data management and statistical analyses

Categorical variables were presented as frequencies and percentages. We assessed the distribution of quantitative variables using the Shapiro-Wilk test. As most continuous variables were not normally distributed, they were summarized using the median and interquartile range (IQR). Comparisons between patients who died and those who recovered from coma were made using Pearson's chi-square test (or Fisher's exact test when at least one expected cell size was <5) for categorical data, whereas quantitative data were compared using the Mann-Whitney test.

A simple logistic regression was used to evaluate the association between intrahospital mortality (as the outcome) and different factors (regressors) by computing the crude odds ratio (cOR) with its 95% confidence interval (95%CI). To identify independent predictors of intrahospital mortality, we created a multivariable logistic regression model that included all regressors with a p-value <0.20 according to the simple logistic regression. A multicollinearity test was conducted to assess the potential correlation between the independent variables by computing the variance inflation factor (VIF). A VIF greater than 10 was suspected to indicate multicollinearity. The results of the model were reported as adjusted odds ratios (aOR) and their corresponding 95%CI.

Statistical significance was defined at $p < 0.05$, and statistical analyses were performed using the Epi Info software version 7.2.4.0 (CDC, Atlanta, GA, USA) and the R software version 4.0.3 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

2.5. Ethical considerations

The study protocol was approved by the institutional Health Ethics Committee (Comité Institutionnel d'Ethique de la Santé [CIES]) of the Université Catholique de Bukavu (Ethical approval code: UCB/CIES/NC/015/2021). All procedures performed in this study were in accordance with the 1964 Declaration of Helsinki and its later amendments, and followed national and international ethical standards. The need for informed consent was waived by the ethics committee because this study used retrospective data and included no personal or identifiable information from any of the participants.

3. Results

3.1. General characteristics of the studied population

Sociodemographic and relevant clinical parameters of the study population are summarized in Table 1. A total of 219 adult patients (median age: 49 years, IQR: 33–61 years), predominantly men (62.8%, sex-ratio: 1.69 males per female), were included in this study. Most of these patients (64.9%) had been transferred from other health institutions (either a hospital [56.2%] or a primary healthcare center [8.7%]), while only 35.2% came directly from their homes. Approximately a third of the patients (30.3%) reported having used traditional medicinal plants before their hospital admission. The coma onset was sudden for 25.6% of patients, and progressive (within hours to several days) in 74.4% of them. The median time from coma onset to admission was 24 h (IQR:10–48 h). Symptoms frequently associated with coma included headache (53.9%), fever (38.5%), vomiting (35.2%), and seizures (13.7%). A medical history of arterial hypertension was found in 33.9% of patients, while 21.6% had a history of diabetes mellitus, 6.0% had a known infection by HIV, and only 1.4% were epileptic.

On clinical examination, the patients had a median GCS score of 7 (IQR: 6–8), a heart rate of 102 bpm (IQR: 78–112), a respiration rate of 24 cpm (IQR: 22–28), a systolic blood pressure of 120 mmHg (IQR: 100–190), a diastolic blood pressure of 74 mmHg (IQR: 60–110), a temperature of 36.9 °C (IQR: 36.2–38.0), and a SaO2 of 92% (IQR: 88–95), with 32.4% of them presenting with hypoxemia (defined as a SaO2 below 90%). On neurological examination, 27.9% of the patients had a focal neurological deficit, 22.4% had meningismus (nuchal rigidity, Kernig's sign, or Brudzinski's sign), and 25.1% had a papillary edema on the fundus oculus.

Concerning biological parameters at admission, the patients had a median white blood cell (WBC) count of 9500 elements/μL (IQR: 6200–12,700), with 7100 neutrophils/μL (IQR: 4100–10,100) and 1800 lymphocytes/μL (IQR: 1100–2300). The median neutrophil-to-lymphocyte ratio was 3.85 (IQR: 2.41–6.52). The median hemoglobin level was 14.1 g/dL (IQR: 11.3–15.6), with almost a third of

the patients (31.6%) having anemia. The median serum creatinine level was 1.25 mg/dL (IQR: 1.10–1.95), with 42.8% of the patients exhibiting impaired renal function (defined as a glomerular filtration rate below 60 mL/min/1.73 m^2).

3.2. Causes of non-traumatic coma in patients admitted to the intensive care unit

The different causes of NTC identified in this study are summarized in Table 2. Overall, 55.7% of the patients included in this study had coma due to a structural cause, while systemic (or diffuse) causes accounted for the remaining 44.3%.

Among structural causes, stroke was the most prevalent pathology associated with coma in the study population (25.7% of all patients), followed by meningoencephalitis (16.0%), and cerebral malaria (14.2%). Only two patients (0.91%) had a brain tumor. Out of 55 patients with stroke, 39 (72.2%) had a confirmed hemorrhagic stroke, 11 (20.4%) had an ischemic stroke, and 4 (7.4%) had a stroke of undetermined origin, as no brain imaging was performed. On the other hand, out of the 35 cases of meningoencephalitis, 14 (40.0%) occurred in patients immunocompromised due to HIV infection.

Acute (metabolic) complications of diabetes mellitus were the most common systemic cause of NTC in the study population, accounting for 21.9% of all cases. Among them were hypoglycemia (20 patients, 9.13% of all causes of coma), diabetic ketoacidosis (17 patients, 7.76%), and hyperosmolar hyperglycemic state (11 patients, 5.02%). Other metabolic causes included hepatic encephalopathy in 15 patients (6.85%) and uremic encephalopathy in two patients (0.91%). Hypertensive emergencies accounted for 5.48% of all causes (n = 12 patients), of which nine had hypertensive encephalopathy and three had eclampsia. Coma was attributed to septic shock due to infections located outside of the CNS in 11 patients (5.0%), while intoxication was identified as the cause of coma in eight patients (3.65%), half of which were secondary to benzodiazepine abuse (n = 4/8), followed by ethyl coma (n = 2/8) and accidental inhalation of carbon monoxide (n = 2/8). Finally, one patient (0.46%) was admitted for coma following cardiac arrest, and the remaining one (0.46%) for status epilepticus.

3.3. Vital outcomes and predictors of short-term mortality

Approximately one-third of the patients admitted for coma died during their stay in the ICU (35.2%, 77 out of 219 patients), of whom 26 died within 48 h after admission. The remaining 142 patients recovered from coma and were discharged alive from the ICU.

When comparing different demographic and clinical characteristics between patients who died during their hospitalization and those who recovered, we found that in-hospital mortality was significantly associated with a lower CGS score at admission (median GCS score of patients who died: 6 [6–8], median GCS score of those who recovered:, 7 (5–7), $p = 0.0008$), a lower SaO2 (88% (78–93) versus 93% (90–96), $p < 0.0001$), the presence of a focal neurological deficit (49.2% of patients with a focal neurological deficit versus 29.8% of those without, $p = 0.0069$), the presence of a meningismus (61.2% of patients with meningismus versus 27.7% of those without, $p < 0.0001$), and the presence of a papillary edema on fundus oculus (56.5% of patients with papillary edema versus 28.2% of those without, $p = 0.0005$) (Table 3).

Regarding the biological parameters, only the neutrophil-to-lymphocyte ratio (NLR), total calcemia, BUN, and serum creatinine

Table 2
Causes of non-traumatic coma in patients admitted to the intensive care unit (n = 219).

Diagnosis	Frequency (Percentage)
Primary causes	122 (55.7)
Stroke	54 (24.7)
Hemorrhagic stroke	39 (17.8)
Ischemic stroke	11 (5.0)
Undetermined origin	4 (1.8)
Bacterial or fungal meningoencephalitis	35 (16.0)
Associated with HIV infection	14 (6.4)
Cerebral malaria	31 (14.2)
Brain tumor	2 (0.9)
Systemic causes	97 (44.3)
Metabolic complications of Diabetes mellitus	48 (21.9)
Hypoglycemia	20 (9.1)
Diabetic ketoacidosis	17 (7.8)
Hyperosmolar hyperglycemic state	11 (5.0)
Other metabolic causes	17 (7.8)
Hepatic encephalopathy	15 (6.9)
Uremic encephalopathy	2 (0.9)
Hypertensive emergencies	12 (4.9)
Hypertensive encephalopathy	9 (4.1)
Eclampsia	3 (1.4)
Septic shock	11 (5.0)
Intoxications	8 (3.7)
Benzodiazepines abuse	4 (1.8)
Ethylic coma	2 (0.9)
Inhalation of carbon monoxide	2 (0.9)
Status epilepticus	1 (0.46)

were associated with the vital outcomes of the study population (Table 4). Patients who died had a higher NLR (4.37 [2.67–7.00] versus 3.69 [2.17–5.91], p = 0.0458), a higher BUN (41.5 mg/dl [31.1–95.5] versus 36.8 mg/dl (25.0–60.0), p = 0.0076), and higher levels of serum creatinine (1.45 mg/dl (1.20–2.45) versus 1.20 mg/dl (1.00–1.80), p = 0.0014) compared to those who survived, while their total calcemia was significantly lower (2.11 mmol/l [2.00–2.14] versus 2.12 mmol/l [2.01–2.66], p = 0.0377) (Table 4).

Table 5 shows the mortality rates discriminated according to the cause of coma. The mortality rate was significantly higher in patients with a primary cause of coma (43.4%) compared to those with a systemic cause (24.7%, p = 0.0040). Half of the patients (50%) admitted in a coma secondary to stroke died, whereas only 30.3% of those without stroke had a fatal outcome (p = 0.0085). Coma secondary to meningoencephalitis was also associated with a significantly higher mortality rate (60% versus 30.4%, p = 0.0008). On the other hand, cerebral malaria was associated with a significantly lower mortality rate (9.7% versus 39.4%, p = 0.0013). Among patients with systemic causes of coma, there was a trend towards a higher mortality rate in those who developed a coma following septic shock, but the difference did not reach significance (63.6% vs. 33.7%, p = 0.0543). A significantly lower mortality rate was observed in patients admitted in coma associated with diabetic ketoacidosis (5.9% vs. 37.6%, p = 0.0085), hyperosmolar hyperglycemia state (0.0% vs. 37.0%, p = 0.0090), and hypertensive encephalopathy (0.0% vs. 36.7%, p = 0.0241).

Logistic regression analyses are summarized in Figures [1(a, b)]. According to simple logistic regression analysis, the use of traditional medicinal plants prior to admission, the presence of headaches, the depth of coma (GCS score <7), hypoxemia (SaO2 < 90%), a focal neurological deficit, meningismus, papillary edema on fundus oculus, low calcemia, high WBC counts, high neutrophil counts, high NLR, and coma of a primary cause were associated with intrahospital mortality at a p value of <0.20. The white blood cell and neutrophil counts had a VIF higher than 10, suggesting problematic multicollinearity. Thus, the neutrophil count was removed

Table 3
Vital outcome of patients with non-traumatic coma according to demographic and clinical characteristics (n = 219).

Parameters	Improvement (n = 142)	Death (n = 77)	p
Demographics			
Age (years)[a]	50.0 (33.0–62.0)	48.0 (31.5–61.0)	0.9183
Sex			
Female	55 (67.1)	27 (32.9)	0.5923
Male	87 (63.5)	50 (36.5)	
Anamnestic (subjective) information			
Time from onset to admission (hours)[a]	24.0 (12.0–48.0)	36.0 (12.0–48.0)	0.6275
Coma onset			
Sudden	39 (69.6)	17 (30.4)	0.3829
Progressive	103 (63.2)	60 (36.8)	
Use of traditional medicinal plants			
Yes	38 (57.6)	28 (42.4)	0.1391
No	104 (68.0)	49 (32.0)	
Major associated symptoms			
Headaches			
Yes	86 (69.3)	38 (30.7)	0.1099
No	56 (58.9)	39 (41.1)	
Fever			
Yes	61 (62.9)	36 (37.1)	0.5892
No	81 (66.4)	41 (33.6)	
Vomiting			
Yes	53 (63.9)	30 (36.1)	0.8115
No	89 (65.4)	47 (34.6)	
Seizures			
Yes	18 (72.0)	7 (28.0)	0.4257
No	124 (63.9)	70 (36.1)	
Clinical (objective) examination			
GCS[a]	7 (5–7)	6 (6–8)	0.0008
Temperature (°C)[a]	36.9 (36.2–38.1)	36.9 (36.1–37.9)	0.6512
Heart rate (bpm)[a]	104 (84–112)	98 (72–112)	0.2654
Respiratory rate (cpm)[a]	24 (22–28)	24 (24–28)	0.8723
Systolic blood pressure (mmHg)[a]	120 (100–170)	120 (98–190)	0.5528
Diastolic blood pressure (mmHg)[a]	76 (60–98)	72 (56–120)	0.5466
Oxygen saturation (%)[a]	93 (90–96)	88 (78–93)	<0.0001
Neurological deficit			
Yes	31 (50.8)	30 (49.2)	0.0069
No	111 (70.2)	47 (29.8)	
Meningismus			
Yes	19 (38.8)	30 (61.2)	<0.0001
No	123 (72.3)	47 (27.7)	
Papillary edema[b]			
Yes	20 (43.5)	26 (56.5)	0.0005
No	97 (71.8)	38 (28.2)	

[a] Data were presented as medians and interquartile ranges. All other parameters are expressed as frequencies with corresponding percentages.
[b] n = 181 because patients with missing information were excluded from the analyses.

Table 4
Vital outcome of patients with non-traumatic coma according to biological characteristics.

Parameters	Improved	Dead	p
Total blood count (n = 217)			
White blood cell count (x1000/μL)	9.25 (5.90–12.2)	9.70 (7.10–13.6)	0.1589
Neutrophiles (x1000/μL)	6.85 (3.70–10.0)	7.80 (4.80–10.7)	0.0893
Lymphocytes (x1000/μL)	1.75 (1.20–2.30)	1.90 (1.10–2.50)	0.7443
Neutrophiles to lymphocytes ratio	3.69 (2.17–5.91)	4.37 (2.67–7.00)	0.0458
Platelets count (x1000/μL)	224.0 (154.0–312.0)	231.0 (135.0–339.0)	0.9380
Hemoglobin (g/dL)	14.2 (11.4–15.7)	13.8 (10.9–15.6)	0.5257
Kidney function (n = 215)			
Blood urea nitrogen (mg/dL)	36.8 (25.0–60.0)	41.5 (31.1–95.5)	0.0076
Serum creatinine (mg/dL)	1.20 (1.00–1.80)	1.45 (1.20–2.45)	0.0014
Serum electrolytes (n = 215)			
Potassium (mmol/L)	4.42 (4.06–5.04)	4.60 (4.13–5.22)	0.2306
Natrium (mmol/L)	139.3 (135.8–143.2)	138.6 (135.6–144.0)	0.7776
Chloride (mmol/L)	106.1 (100.7–110.2)	104.0 (100.2–109.8)	0.4257
Calcium (mmol/L)	2.12 (2.01–2.66)	2.11 (2.00–2.14)	0.0377

Table 5
Vital outcome of patients with non-traumatic coma according to coma etiologies (n = 219).

Diagnosis	Death (n, %)	Improvement (n, %)	p
Types of etiology			
Primary causes	53 (43.4)	69 (55.6)	0.0040
Systemic causes	24 (24.7)	73 (75.3)	
Primary causes			
Meningoencephalitis			
Yes	21 (60.0)	14 (40.0)	0.0008
No	56 (30.4)	128 (69.6)	
Stroke			
Yes	27 (50.0)	27 (50.0)	0.0085
No	50 (30.3)	115 (69.7)	
Cerebral malaria			
Yes	3 (9.7)	28 (90.3)	0.0013
No	74 (39.4)	114 (60.6)	
Systemic causes			
Complications of Diabetes mellitus			
Yes	5 (10.6)	42 (89.4)	<0.0001
No	72 (41.9)	100 (58.1)	
Hepatic encephalopathy			
Yes	8 (53.3)	7 (46.7)	0.1267
No	69 (33.8)	135 (66.2)	
Hypertensive encephalopathy			
Yes	0 (0.0)	9 (100.0)	0.0241
No	77 (36.6)	133 (63.3)	
Septic shock			
Yes	7 (63.6)	4 (36.4)	0.0543[a]
No	70 (33.7)	138 (66.4)	
Intoxications			
Yes	0 (0.0)	8 (100.0)	0.053[a]
No	77 (36.5)	134 (63.5)	

[a] Fischer exact test.

from the model, retaining only the total white blood cell count. Multiple logistic regression analyses determined that short-term mortality was significantly and independently associated with elevated serum creatinine (aOR 1.64, 95%CI: 1.17–2.29, p = 0.0042), the use of traditional medicinal plants (aOR 2.82, 95%CI: 1.16–6.86, p = 0.0223), a GCS score <7 (aOR 4.30, 95%CI: 1.73–10.71, p = 0.0017), hypoxemia (aOR 3.99, 95%CI: 1.71–9.28, p = 0.0013), and the presence of meningismus (aOR 3.86, 95%CI: 1.41–10.55, p = 0.0084), after controlling for potential confounders (seeFig. 1 and Supplementary Material Tables S1 and S2).

4. Discussion

This study aimed to identify the most common causes and prognostic factors of NTC at a tertiary hospital in Bukavu, eastern DRC. Its findings revealed that stroke, acute metabolic complications of diabetes mellitus, and primary brain infections (meningoencephalitis and cerebral malaria) are the most common causes of NTC in this particular setting. Over one-third of the patients (35.2%) admitted to the ICU for NTC died during their ICU stay. This high mortality rate was significantly and independently associated with a GCS score of <7, the presence of meningismus at clinical evaluation, hypoxemia, consumption of traditional herbal medicines prior to

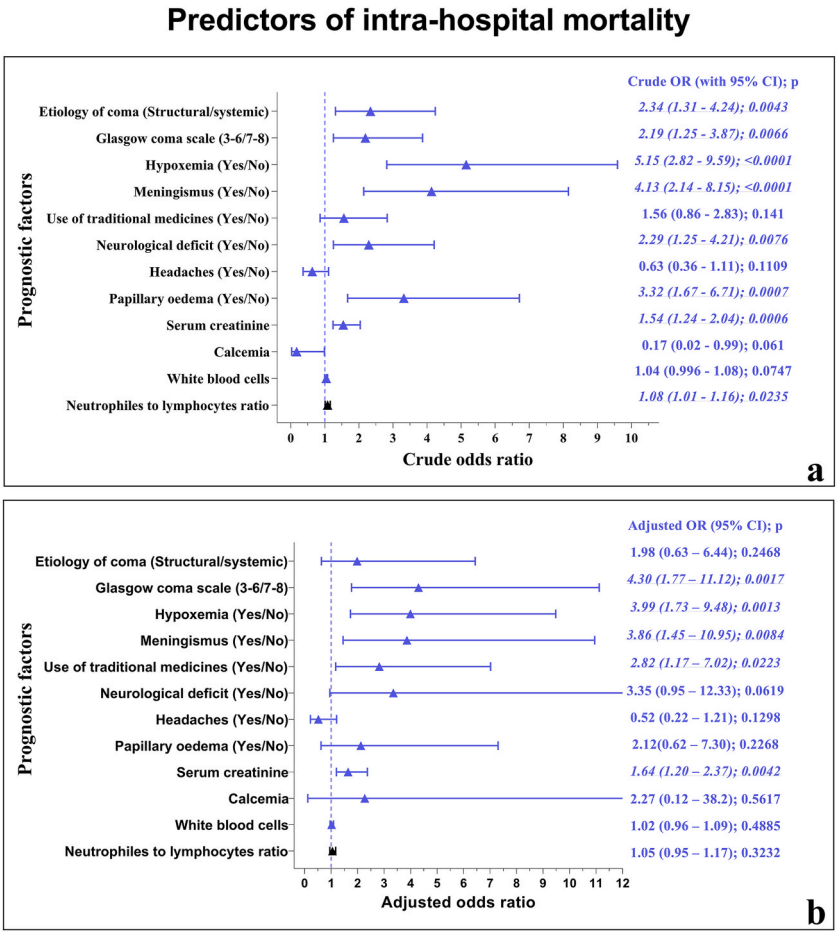

Fig. 1. Predictors of intrahospital mortality. (a) Simple logistic regression analyses, presenting crude odds ratio with 95% confidence intervals. **(b)** Multiple logistic regression analyses showing adjusted odds ratio with 95% confidence intervals.

hospital admission, and elevated serum creatinine levels.

4.1. Causes of non-traumatic coma in patients admitted to the intensive care unit

NTC is a common reason for ED and ICU admission [21,22]. Identifying the etiology of NTC is a key step in the management of this life-threatening medical condition, especially in resource-limited settings, as proper management should combine resuscitation measures with appropriate etiological treatment [23]. Furthermore, vital and functional prognoses are largely influenced by the cause of the coma [24,25]. Several classifications of the etiologies of NTC exist; however, the distinction between primary (or structural) and systemic (non-structural or diffuse) causes based on whether a structural local lesion exists in the brain is one of the most widely used classifications [9,20].

According to this classification, 55.7% of the patients included in this study had a coma secondary to a primary cause, whereas systemic causes accounted for the remaining 44.3%. Stroke was the leading cause of admission for NTC during the study period, followed by acute metabolic complications of diabetes mellitus, and primary CNS infections (including cerebral malaria and meningoencephalitis).

This observation emphasizes the epidemiological transition occurring in developing countries, which are facing an increasing burden of noncommunicable diseases following a rapid urbanization, changes in dietary habits, and an aging population [26,27]. These include cerebrovascular disorders and cardiovascular risk factors (particularly diabetes and arterial hypertension, along with their complications) [28,29]Several community-based studies in the DRC have reported an increase in the prevalence of major cardiovascular risk factors (mainly arterial hypertension, diabetes mellitus, and metabolic syndrome) in recent decades, especially in South-Kivu, in the eastern part of the country [30–32]. In addition to being frequent in this region, diabetes mellitus and arterial hypertension are usually poorly controlled in several African countries [33–36], and this may explain, at least in part, the leading place of stroke and diabetes complications as the identified causes of coma in this study.

The available literature shows that stroke has become a major public health problem and one of the most common causes of

admission for neurological disorders in several sub-Saharan African countries [27,37]. In a cohort study by Laiser et al. [38] that aimed to determine the most common neurological disorders among adults in a Northern Tanzanian hospital, coma (defined as a GCS score <9/15) was the most frequent neurological symptom, found in 95 out of 337 patients, and stroke was the most frequent diagnosis (in 129 out of 337 patients). Additionally, Obiako et al. [39] identified stroke and acute diabetes emergencies as the two leading causes of coma in a cohort of 200 adult patients consecutively admitted for NTC at the emergency unit of a Nigerian hospital between August 2004 and March 2005.

However, in addition to the increase in the burden of noncommunicable diseases, infectious diseases remain prevalent in sub-Saharan Africa and are exacerbated by poverty, prolonged armed conflicts, and other humanitarian crises in the region [27]. Of these, malaria is assumed to be the most frequent infectious disease in this region [40]. In 2021, over 90% of all cases of malaria occurred in Africa, with only four countries (Nigeria, the DRC, Uganda, and Mozambique) accounting for approximately half of the total cases worldwide [41]. Acute bacterial meningitis is another major public health concern in several countries from sub-Saharan Africa. Its prevalence in this region is estimated to be up to ten times higher than in developed countries [42]. Thus, considering that coma is a common clinical presentation of both meningoencephalitis and cerebral malaria [43,44], it is not surprising to find that both diseases were among the leading causes of coma in our study, accounting for approximately 30% of all cases of coma.

Psychoactive substance abuse (mainly benzodiazepines and alcohol) was another cause of admission for NTC in the ICU unit. Substance misuse and abuse are becoming major threats to public health in several African countries, but are still being neglected [45]. The lack of stringent regulatory measures to control the prescription and delivery of psychoactive drugs is among the factors that favor the emergence of this problem [46].

4.2. Factors associated with high mortality in comatose patients

This study found a high in-hospital mortality rate among patients admitted for NTC. Approximately a third (35.2%) of all patients suffering from coma that were admitted during the study period died during their stay at the ICU. This is in accordance with the high short-term (within one month) mortality rates reported in previous studies, which vary on average between 25% and 61%, even in developed countries [9,21,23,47].

Coma-related mortality rates vary largely according to etiology. In several studies, coma secondary to structural brain damage seems to have the worst outcome, with coma secondary to stroke having the highest mortality rates, as high as 60%–95% depending on the particular study and country [22,47,48]. In contrast, systemic causes of coma (especially coma secondary to poisoning or metabolic disturbances such as acute metabolic complications of diabetes mellitus) usually have favorable outcomes when appropriately treated [9,49,50]. Similar observations were made in this study. Meningoencephalitis and stroke were associated with the highest mortality rates (60% and 50%, respectively).

It should be mentioned that cerebral malaria, which was among the leading causes of NTC in this study, was surprisingly associated with a relatively low mortality rate compared to other causes of coma. In fact, only less than 10% of patients with cerebral malaria died during their hospital stay. The mortality rate of patients with cerebral malaria was considerably lower than that reported in the literature. Severe malaria, of which cerebral malaria is the most common presentation, is assumed to have a poor prognosis, especially in resource-poor settings [51,52]. Prompt initiation of antimalarial drug treatment in patients fulfilling the WHO diagnostic criteria may have contributed to the favorable outcomes observed in cerebral malaria patients at the ICU of the HPGRB. In fact, coma usually resolves within two to three days in patients with cerebral malaria who receive prompt and appropriate therapy [44].

After controlling for potential confounders, the severity of coma (GCS score of <7), consumption of traditional medicinal plants, presence of meningismus, presence of hypoxemia, and elevated serum creatinine levels were found to be significantly and independently associated with poor outcomes in patients admitted for NTC to the ICU. In previous studies, most of these have been identified as significant prognostic factors in comatose patients. The severity of coma, as assessed by the GCS, has a recognized prognostic value in patients with NTC from various etiologies [25,53–55]. Physicians and other caregivers from several parts of the world use the GCS as a simple, reliable, and affordable tool to predict the outcome of comatose patients and identify those who need special attention and care [25].

A specific finding of this study is the significant association between the consumption of traditional medicinal plants prior to hospital admission and a poor outcome in comatose patients. Due to financial constraints (low income and lack of medical insurance) as well as local beliefs and traditions, many patients resort in the first instance to traditional healers when they fall ill instead of visiting the local hospital. Not only do such practices delay hospital admission and the initiation of appropriate treatment, but they also lead to administration of medicinal plant extracts with poorly characterized side effects to these patients. These products may potentially be toxic, especially to the kidneys. Although several plants are known to have medicinal properties and have been used as traditional remedies for millennia [56], the nephrotoxic potential of traditional herbal medicines is well documented [57,58]. A systematic review and meta-analysis conducted by Stanifer et al. [59] has estimated that 80% of the population in sub-Saharan Africa resorts to herbal or traditional medicines, and that this practice may be responsible for approximately 35% of all new cases of acute kidney injury in the region [59]. In our study, only 30.1% of patients reported having used traditional medicinal plants, which is considerably lower than the 80% reported by Stanifer et al. [59]but close to the percentage recently reported by Masimango et al. [60] in the urban population of South-Kivu, eastern DRC (29.3%). An increase in serum creatinine level, which is suggestive of kidney injury, was independently associated with high mortality in the comatose patients included in this study. Considering the association described in the literature between the use of herbal medicines and kidney damage, and the fact that both factors were independently associated with high odds of mortality in this study, emergency and ICU physicians should be particularly attentive with comatose patients with a history of consumption of such plants and closely monitor their renal function. In addition, this study highlights the need for community

awareness campaigns to address the threats posed by the (mis)use of traditional herbal medicines.

4.3. Strengths and limitations of the study

To the best of our knowledge, this is the first study to investigate the causes and prognostic factors of NTC among adult patients in the DRC. The involvement of specialist physicians (neurologists as well as emergency and critical care physicians) allowed the recruitment of patients who met the international standards for the definition of NTC cases. Furthermore, although the consumption of traditional herbal medicines is a frequent practice in the region, their safety has never been investigated. This study showed that the use of these traditional medicines prior to hospital admission was significantly and independently associated with a high mortality rate in patients admitted for NTC in intensive care.

Finally, this study had several limitations that should be considered when interpreting its findings. Patients were followed-up only until their discharge from the ICU. Some studies have reported a significantly increased mortality rate within a year after hospital discharge in patients who presented with NTC compared with the general population, independently of the etiology of coma [61]. In addition, the generalization of the results of this study may be limited since the main outcome was only "improvement" or "death". In fact, other previously reported adverse outcomes of NTC such as neurological sequelae and cognitive impairment [9], were not evaluated in this study. We did our best to account for potential confounders in the evaluation of prognostic factors. However, owing to the retrospective design of the study and the unavailability of advanced research tools, some prognostic factors could not be included in the regression model. Despite these limitations, this study has the merit of using simple and affordable tools to identify the etiologic and prognostic factors of NTC in a resource-limited setting, which can be applied in several contexts where neurologists, emergency care, and ICU physicians do not have access to sophisticated tools.

5. Conclusion

Clinical neurological examinations, along with simple and affordable paraclinical investigations, may provide sufficient information to determine the etiology of NTC, even in resource-poor settings, and to evaluate the prognosis of comatose patients. Physicians should be aware of poor outcomes in comatose patients and initiate prompt, appropriate, and etiology-driven treatment in order to reduce the high burden of this condition. Particular attention should be paid to patients who present with profoundly altered consciousness, hypoxemia, or meningismus. Kidney function should be monitored in comatose patients, especially in those who have consumed traditional medicines. Finally, considering its high mortality rate, the best management strategy for NTC should consist of primary prevention through early identification and management of the underlying causes, as most of the etiologies identified in this study may be prevented by adopting appropriate measures.

Author contribution statement

Guy-Quesney Mateso: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Samuel Makali, Marius Baguma: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ashuza Shamamba: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Balola Ntaboba, Victoire Urbain, Musingilwa Eric, Emmanuel Murhabazi: Analyzed and interpreted the data; Wrote the paper.

Martine Mihigo: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Pacifique Mwene-Batu: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Landry Kabego: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18398.

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