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Prognostic Signification of Admission Hyperglycemia among Acute Stroke Patients in Intensive Care Units in Kinshasa, the Democratic Republic of the Congo

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Abstract

BACKGROUND AND AIM: Although admission hyperglycemia has been reported to be associated with unfavorable outcomes in acute stroke, little is known about this association in sub-Saharan Africa. Therefore, the aim of the present study was to assess the prognostic significance of admission hyperglycemia in the acute phase of stroke in Congolese patients. METHODS: In a multicenter prospective cohort study, consecutive patients with acute stroke were examined in 5 Emergency Rooms or Intensive Care Units of Kinshasa between July 15th, 2017 and March 15th, 2018. The severity of stroke was assessed at admission using the Glasgow Coma Scale. Stress hyperglycemia was defined as random blood glucose levels at admission > 140 mg/dL in patients without known type 2 diabetes mellitus (T2DM). The endpoint was 10-day all-cause in-hospital mortality. Survival (time-to-death) curves were built using the Kaplan Meier methods. Cox proportional analysis was used to identify predictors of 10-day all-cause in-hospital mortality. The predictive performance of blood glucose level to predict 10-day all-cause in-hospital mortality was assessed using ROC curve analysis. RESULTS: Out of 194 patients (mean age 58.7 ± 13.1 years; 64% males, 74.7% light to moderate stroke severity; 63.4% ischemic stroke) enrolled, 106 (54.6%) had admission hyperglycemia

with 77 (72.6%) having stress hyperglycemia. Ninety four deaths (48.5%); mortality rate of 6 deaths per 100 person-days (95%CI 2.7 - 9.3) occurred during a median follow up time 6 (5 - 7) days equivalent to 1542 person-days. Independent predictors of 10-day all-cause in-hospital mortality were admission hyperglycemia regardless of diabetes status (aHR 3.77; 95%CI 1.92 - 7.42; $p < 0.001$), GCS < 8 (aHR 2.87; 95%CI 1.57 - 5.23; $p = 0.001$) and non-use of mechanical ventilation (aHR 1.97; 95%CI 1.05 - 3.70; $p = 0.034$). Blood glucose concentrations (AUC 0.743; 95%CI 0.672 - 0.814) had a better predictive performance for 10-day all-cause in-hospital mortality with an optimal value of 154 mg/dL (sensitivity 76.6% and specificity 70%). CONCLUSION: More than half of critically ill stroke patients exhibit admission hyperglycemia that impacts negatively on their survival in the acute phase highlighting thus the need for a better blood glucose control to improve outcomes.

Keywords

Admission Hyperglycemia, Stroke, Prognostic Significance, Black Africans

1. Introduction

Stroke, a common clinical problem in emergency department, is associated with an increased risk of death, particularly in its acute phase highlighting thus the need for the search and control of potential predictors of mortality [1]. Among potential predictors, admission hyperglycemia has been reported to be a substantial contributor [1]. Indeed, increased admission blood glucose levels in acute stroke have been reported to be associated with longer in-hospital stay, increased costs and mortality [1] [2]. Hyperglycemia is found in more than half of patients with stroke with most of them not having a known history of diabetes mellitus [1] [2]. In some patients, hyperglycemia is considered a reflection of preexisting but unrecognized diabetes mellitus; however, more often, it is the result of an acute stress response, typically termed stress hyperglycemia [1] [2]. The toxic effects of hyperglycemia to the brain tissue are thought to rely upon several biochemical and hemodynamic mechanisms including the accumulation of lactic acid due to anaerobic metabolism, enhanced glutamate release, and increased cerebral edema [1] [2] [3]. Therefore, the evaluation of the relative contribution of admission hyperglycemia to the risk of death in the acute phase of stroke could help improve the outcome of patients with acute stroke [1] [2] [3].

In the Democratic Republic of the Congo (DRC), stroke is a common clinical finding in ICU and is associated with poor outcomes [4] [5] [6] [7] [8]. If the relationship between admission hyperglycemia and mortality has been already studied in stroke patients [5], it is not yet the case for those in the acute phase of stroke. Therefore, the aim of the present study was to assess the impact of admission hyperglycemia on outcome of stroke patients at the acute phase admit-

ted in ICUs in Kinshasa, the capital City.

2. Methods

From July 15, 2017 to March 15, 2018, we conducted a multicenter prospective observational study searching for admission hyperglycemia and its impact on survival of patients admitted for acute stroke in 5 Intensive Care Units (ICUs, University of Kinshasa Hospital, Ngaliema Clinics, Mother & Child Center Monkole, Biamba Marie Mutombo Hospital, Ngaliema Medical Center) in Kinshasa, the Capital City of the Democratic Republic of the Congo (DRC). Inclusion criteria were as follows: age ≥ 18 years, stroke suspected clinically according to WHO recommendations [9] and confirmed by computerized tomography and informed consent. Were excluded patients without available blood glucose measurement or brain computerized tomography and those with transient ischemic attack. Data related to outcome were vital status and survival (time-to-death) during the acute phase of stroke defined as the first 10 days post-stroke. Demographic (age, gender, education level), past medical history and clinical characteristics were recorded at the time of enrollment. Initial stroke severity was evaluated on the first day of admission on the basis of the Glasgow Coma Scale (GCS) and classified as light to moderate (GCS > 8) and severe (GCS ≤ 8). Laboratory data on admission included non-fasting blood glucose, hemoglobin, hematocrit, white blood cells, blood urea nitrogen (BUN), serum creatinine, uric acid, cholesterol and its sub-fractions, serum triglycerides, serum electrolytes and were determined using usual techniques in the Central Laboratory of each participating ICU Admission random glucose was the first non-fasting plasma glucose measured using an enzymatic method at the central laboratory of each participating ICU. According to the American Diabetes Association (ADA) guidelines, hyperglycemia was defined as blood glucose > 7.8 mmol/L (>140 mg/dL) and classified as acute (stress) hyperglycemia [random blood glucose > 7.8 mmol/L (>140 mg/dL) without evidence of previous diabetes] and chronic [in the absence of glycated hemoglobin, random blood glucose > 7.8 mmol/L (>140 mg/dL) with evidence of previous diabetes [10]. Hypertension was defined as a known previous diagnosis of hypertension or current use of antihypertensive drugs. Diabetes was defined as a history of known diabetes or current use of oral antidiabetic drugs or insulin.

3. Statistical Analysis

Baseline characteristics were summarized as mean (standard deviation) or median (interquartile range) for continuous variables and as number (%) for categorical variables. Independent associations between baseline characteristics and hyperglycemia, defined as level of blood glucose ≥ 140 mg/dL were examined in multivariable logistic regression models with all significant baseline variables. Kaplan Meier method was used to describe survival over 10 days post stroke in the group as a whole and according to type of hyperglycemia, hyperglycemia and

stroke type, hyperglycemia and stroke severity and insulin treatment status. Patients who survived at 10 days were censored. Difference between survival curves by admission hyperglycemia status was described using the Log-rank test. Cox proportional hazard modeling was used to assess independent predictors of 10-day all-cause in-hospital mortality with a special emphasis on admission hyperglycemia. Receiver operating characteristic (ROC) analysis was conducted for evaluating the predictive performance (Area Under the Curve) of the admission random glucose as a continuous variable to discriminate favorable and poor outcomes. P value < 0.05 defined the level of statistical significance. The study was approved by the Ethical and Research Committee of Kinshasa School of Public Health and received the authorization of the Medical Staff of the different ICUs and Emergency Rooms involved in the present study.

4. Results

Sociodemographic and clinical characteristics of the study population as a whole and according to blood glucose status are summarized in **Table 1**. One hundred ninety four patients (64% males) with acute stroke were consecutively included in the present study. Their mean age was 58.7 ± 13.1 years with a half of them aged ≥60 years. History of hypertension and diabetes was reported by 126 (64.9%) and 32 (16.5%) patients, respectively. In most of patients (75.3%) care was supported by themselves or their family.

Admission hyperglycemia was observed in 106 (54.6%) patients with the majority of them (n = 77; 72.6%) having stress hyperglycemia. Compared to patients without hyperglycemia, those with hyperglycemia had a significantly higher proportion (55.7% vs 40.9%; p = 0.028) of patients aged ≥ 60 years (**Table 1**).

Table 2 summarizes the biologic parameters of the study population as a whole and according to blood glucose status. In the entire group, average levels of blood glucose and eGFR were 182.4 ± 27.5 mg/dL and 70.2 ± 47.5 mL/min/1.73 m^2, respectively. Compared to patients without hyperglycemia, those with hyperglycemia had in average significantly lower eGFR levels (76.6 ± 49.4 vs 57.0 ± 40.4 mL/min/1.73 m^2; p = 0.01).

Stroke characteristics and treatment prescribed to the study population as a whole and according to blood glucose status are given in **Table 3**. In the whole group, ischemic and hemorrhagic strokes were observed in 115 (59.3%) and 71 (36.6%) patients, respectively. Symptoms most frequently reported were loss of consciousness (75.5%), motor deficiency (24.7%) and seizures (13.9%). The average interval between stroke occurrence and medical admission was 30.1 ± 3.0 hours. Computerized brain tomography was performed within 6 - 12 hours, 12-24 hours and ≥24 hours in 39 (17.9), 93 (42.7%) and 88 (39.4%) patients, respectively. GCS ≥ 8 and <8 were observed in 145 (74.7%) and 49 (25.3) patients, respectively. The average Sp02 was 90.8 ± 9.6 with the majority (n = 150; 77.3%) having values ≥ 90%. Antihypertensive (mainly nicardipine), anti-edematous

Table 1. Sociodemographic and clinical characteristics of stroke patients as a whole and according to hyperglycemia status.

Variables	All n = 194	No Hyperglycemia n = 88	Hyperglycemia n = 106	P
Age, years	58.7 ± 13.1	57.0 ± 11.3	60.1 ± 14.3	0.099
				0.028
<60, n (%)	95 (49)	52 (59.1)	47 (44.3)	
≥60, n (%)	99 (51)	36 (40.9)	59 (55.7)	
Gender, n (%)				0.497
Males	129 (64)	58 (65.9)	71 (67.0)	
Females	65 (46)	30 (34.1)	35 (33.0)	
Educational level, n (%)				0.394
None	23 (11.9)	12 (13.6)	11 (10.4)	
Primary/secondary	99 (51.0)	39 (44.3)	60 (54.6)	
High	72 (37.1)	37 (42.0)	35 (33.0)	
Care financial support, n (%)				0.028
Patient/family	146 (75.3)	60 (68.2)	86 (81.1)	
Employers/Insurance/public sector	48 (24.7)	28 (31.8)	20 (18.9)	
Diabetes, n (%)	32 (16.5)	3 (3.4)	27 (27.4)	<0.001
Diabetes duration, years	7.7 ± 2.3	6.6 ± 2.3	7.8 ± 2.2	0.680
Type of hyperglycemia, n (%)				
Acute (stress) hyperglycemia	-	-	77 (72.6)	
Chronic hyperglycemia	-	-	29 (27.4)	
Hypertension, n (%)	126 (64.9)	55 (62.5)	71 (67.0)	0.308
Hypertension duration, years	7.8 ± 2.3	7.1 ± 2.8	8.3 ± 2.6	0.214
Previous stroke, n (%)	38 (19.6)	18 (20.5)	20 (18.9)	0.853
Physically active, n (%)	14 (7.2)	8 (9,1)	6 (5.7)	0.260
Alcoholintake, n (%)	44 (22.7)	20 (18.9)	24 (27.3)	0.029
Smoking, n (%)	16 (8.2)	6 (6.8)	10 (9.4)	0.348
SBP, mmHg	168.1 ± 37.5	164.7 ± 38.5	171.3 ± 36	0.161
DBP, mmHg	96.6 ± 23.0	93.9 ± 23.2	99.2 ± 22.6	0.064
MAP, mmHg	120.4 ± 26.1	117.5 ± 25.9	123.3 ± 26.1	0.079
PP, mmHg	71.5 ± 25.0	70.9 ± 28.3	72.1 ± 21.5	0.687
HR, bpm	92.5 ± 23.9	92.9 ± 23.6	92.1 ± 24.3	0.763

Data are expressed as mean ± standard deviation, absolute (n) and relative (%) frequency. Abbreviations: SBP, systolic blood pressure DBP, diastolic blood pressure MAP, mean arterial blood pressure PP, pulse pressure HR, heart rate bpm, beat per minute.

(mainly mannitol), anti-seizure (mainly phenobarbital), mechanical ventilation and insulin therapy were prescribed in 113 (58.2), 72 (37.1), 71 (36.5%), 50 (25.7%) and 33 (17%) patients, respectively. Apart from insulin therapy, the

Table 2. Biological parameters of stroke patients as a whole and according to hyperglycemia status.

Variables	N	All n = 194	No Hyperglycemia n = 88	Hyperglycemia n = 106	P
Glucose, mg/Dl	194	182.4 ± 27.5	196.0 ± 23.9	186.6 ± 26.3	0.343
WBC, /µL	132	14206.5 ± 269.6	10502.9 ± 242.8	13051.9 ± 225.8	0.323
N, %	138	71.4 ± 21.6	69.9 ± 19.5	70.9 ± 20.9	0.659
L, %	132	21.6 ± 15.9	20.3 ± 10.8	21.2 ± 14.4	0.609
Creatinine, mg/dL	150	4.1 ± 0.9	3.6 ± 0.7	3.9 ± 0.8	0.681
eGFR, mL/min/1.73 m^2	150	70.2 ± 47.5	76.6 ± 49.4	57.0 ± 40.4	0.017
BUN, mg/dL	150	58.6 ± 5.9	79.2 ± 9.0	64.9 ± 7.1	0.067
Uricacid, mg/dL	22	7.6 ± 1.6	7.6 ± 4.2	7.6 ± 3.7	0.989
K^+, mEq/L	110	4.2 ± 0.6	4,04 ± 0.73	4,2 ± 0,7	0.183
Na^+, mEq/L	89	138.5 ± 9.7	138.7 ± 40.9	134.1 ± 25.7	0.227
HCO_3, mEq/L	29	20.8 ± 5.3	22.1 ± 5.1	18.1 ± 5.7	0.074
Cl^-, mEq/L	38	102.7 ± 9.4	98.5 ± 8.9	104,6 ± 9.9	0.043
Calcium, mEq/L	36	2.9 ± 0.4	3.02 ± 03	3.9 ± 0.3	0.298
Ca^{++}, mEq/L	10	1.7 ± 0.6	1.8 ± 0.8	1.3 ± 0.1	0.136

Data are expressed as mean ± standard deviation, absolute (n) and relative (%) frequency. Abbreviations: WBC, white blood cell N; neutrophils L, lymphocyte eGFR, estimated glomerular filtration rate K^+ potassium Na^+; sodium HCO_3, bicarbonates Cl^-, chloride Ca^{++}, ionized calcium.

Table 3. Stroke characteristics of the study population as a whole and according to hyperglycemia status.

Variables	All n = 194	No Hyperglycemia n = 88	Hyperglycemia n = 106	P
Symptoms at admission, n (%)				
Loss of consciousness	146 (75.3)	61 (69.3)	85 (80.2)	0.057
Impotence	48 (24.7)	25 (28.4)	23 (21.7)	0.181
Seizures	27 (13.9)	15 (17.0)	12 (11.3)	0.174
Vomiting	6 (3.1)	2 (2.3)	4 (3.8)	0.433
Time Interval event-ICU admission, hour	30.1 ± 3	28.9 ± 3.1	31.1 ± 3.2	0.595
Time interval event-brain CT scan, n (%)				0.450
6 - 12 h	15 (7.7)	5 (5.7)	10 (9.4)	
12 - 24 h	93 (47.9)	40 (45.5)	53 (50.0)	
≥24 h	86 (44.3)	43 (48.8)	33 (31.1)	
Stroke type, n (%)				0.115
Hemorrhagic	71 (36.6)	39 (44.3)	32 (30.2)	
Ischemic	115 (59.3)	49 (55.6)	69 (65.1)	
Others	8 (4.1)	3 (4.1)	5 (4.7)	

Continued

Temperature, ˚C	40.6 ± 3,5	40.7 ± 6.6	40,5 ± 4,9	0.971
Respiratory rate, cpm	23.7 ± 5.8	23.5 ± 5.8	23.9 ± 5.9	0.531
GCS	10.6 ± 3.4	11.5 ± 3.0	9.9 ± 3.5	<0.001
				<0.001
<8	49 (25.3)	10 (11.4)	39 (36.8)	
≥8	145 (74.7)	78 (88.6)	67 (63.2)	
Sp02, %	90,8 ± 9.6	10.5 ± 3.5	11.6 ± 2.7	0.183
				0.297
<90	44 (22.7)	22 (25.0)	22 (20.8)	
≥90	150 (77.3)	66 (75.0)	84 (79.2)	
Pupilla status, n (%)				0.916
Bilateral myosis	28 (14.4)	13 (14.8)	15 (14.2)	
Bilateral mydriasis	22 (11.3)	11 (12.5)	11 (10.4)	
Motor deficiency, n (%)	120 (61.9)	57 (64.8)	63 (59.4)	0.270
Treatment, n (%)				
CCB (Nicardipine)	113 (58.2)	64 (72.7)	70 (66.0)	0.199
Insulin	43 (22.2)	0 (0.0)	43 (40.6)	0.007
Anti-seizure (Phenobarbital)	71 (36.5)	32 (36.4)	39 (36.8)	0.536
Anti-edematous (Mannitol)	72 (37.1)	26 (29.5)	46 (43.4)	0.003
Catecholamines	33 (17.0)	9 (10.2)	24 (22.6)	0.057
Mechanical ventilation	50 (25.7)	17 (19.3)	33 (31.1)	0.043

Data are expressed as mean ± standard deviation, absolute (n) and relative (%) frequency. Abbreviations: CT, computed tomography ˚C, Celsius degree GCS, Glasgow coma scale Sp02, peripheral oxygen saturation CCB, calcium channel blocker.

proportion of patients prescribed anti-edematous therapy was significantly higher (43.4 vs 29.5%; p = 0.003) in patients with hyperglycemia compared to those without hyperglycemia (**Table 3**).

Among 194 study subjects, 94 deaths (48.5%) equivalent to 6 deaths per 100 person-days (95%CI 2.7 - 9.3) occurred within the first 10 days [median follow up time 6 (5 - 7) days equivalent to 1542 person-days]. Of the 94 deaths, 73 (68.9%) occurred among hyperglycemic patients (n = 106) with 55 (51.9%) and 18 (17.0%) deaths among patients with stress and chronic hyperglycemia, respectively (**Table 4**). The survival in the whole group is depicted in **Figure 1**. Survival decreased overtime with values of 85.9% and 52.3% at days 2 and 10 after admission, respectively. With reference to blood glucose status (**Figure 2**), the survival was significantly better in patients without hyperglycemia (p < 0.001) in comparison to those with hyperglycemia. The survival was also better in stroke patients with GCS ≥ 8 (p < 0.001) in comparison to those with stroke and GCS < 8 (**Figure 3**). Hyperglycemic stroke patients without known diabetes

Table 4. Outcomes in the study population as a whole.

Blood glucose	N	Vital status	
		Alive	Deceased
<150 mg/dL, n (%)	88	67 (76.1)	21 (23.9)
≥150 mg/dL, n (%)	106	33 (31.1)	73 (68.9)
-Stress HG, n (%)	77	22 (20.7)	55 (51.9)
-ChronicHG, n (%)	29	11 (10.4)	18 (17.0)
Total	194	100 (51.5)	94 (48.5)

Data are expressed as absolute (n) and relative (in percent) frequency. Abbreviations: HG, hyperglycemia.

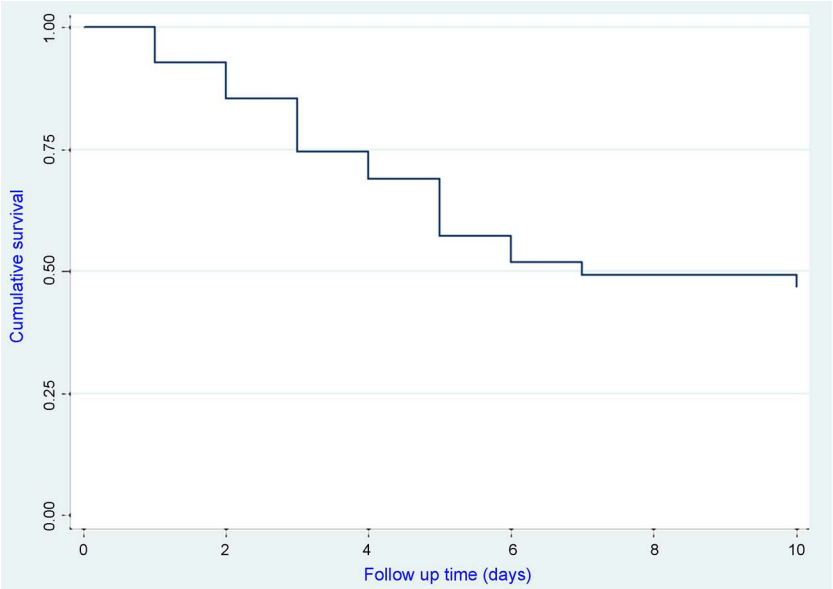

Figure 1. Survival curve of the study population as a whole.

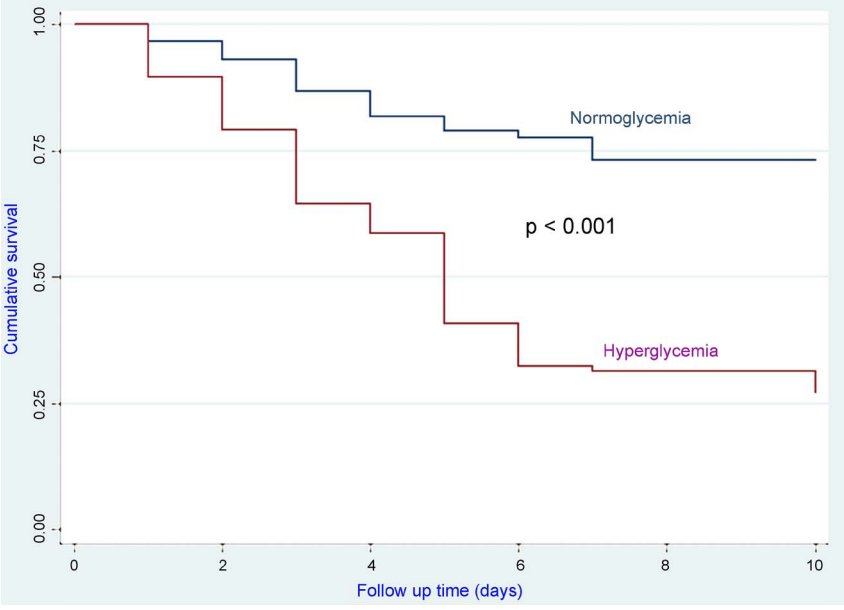

Figure 2. Survival curves of the study population according to blood glucose status.

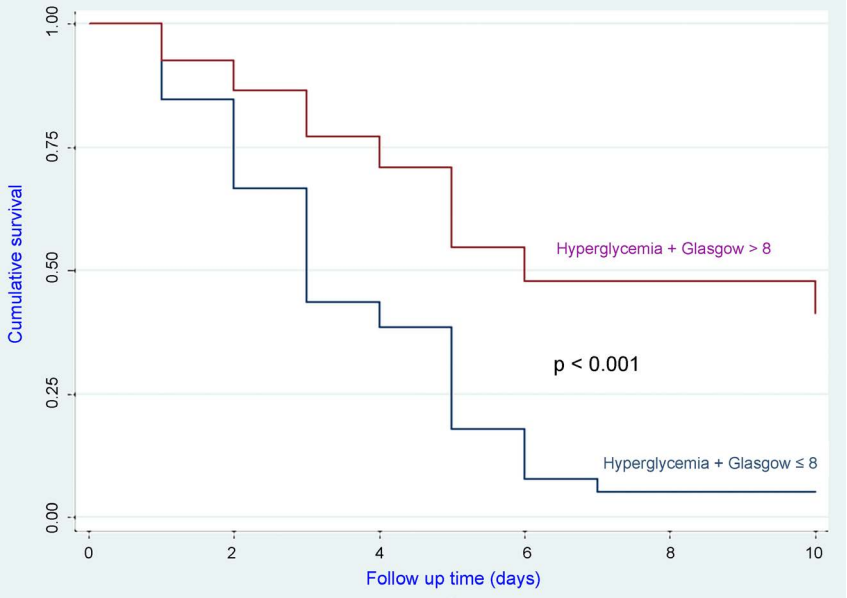

Figure 3. Survival curves of the study population according to blood glucose status and severity of stroke.

tended to have a worst survival than those with known diabetes (chronic hyperglycemia); however, the difference was not statistically significant.

Predictors of 10-day all-cause in-hospital mortality in the entire group are depicted in **Table 4**. In addition to stroke severity [GCS < 8 (aHR 2.87; 95%CI 1.57 - 5.23; p = 0.001)] and non-use of mechanical ventilation (aHR 1.97; 95%CI 1.05 - 3.70; p = 0.034), admission hyperglycemia (aHR 3.77; 95%CI 1.92 - 7.42; p < 0.001) emerged as one of the main independent predictors of 10-day all-cause in-hospital mortality mortality.

The performance of blood glucose concentrations as a continuous variable in predicting 10-day all-cause in-hospital mortality is shown in **Figure 4**. With an area under the curve (AUC) of 0.743 [IC 95% (0.672 - 0.814)], blood glucose concentrations have shown a good performance in predicting 10-day all-cause in-hospital mortality in the present study. The cutoff value of admission blood glucose level with the highest sensitivity and specificity in predicting all-cause in-hospital mortality was 154 mg/dL (sensitivity = 76.6%, specificity = 70.0%).

5. Discussion

The main findings of the present study are as follows: first, survival was significantly worst in stroke patients with hyperglycemia and those with hyperglycemia and severe stroke; second, patients with stress hyperglycemia tended to experience a worst survival than those with chronic hyperglycemia (known diabetes); third, more than half of patients died in the present study with stroke severity, non-use of mechanical ventilation and hyperglycemia as the main independent predictors of 10-day all-cause in-hospital mortality in patients with predominantly mild to moderate stroke severity; fourth, admission blood glucose concentrations had a good predictive performance with 154 mg/dL as the cutoff

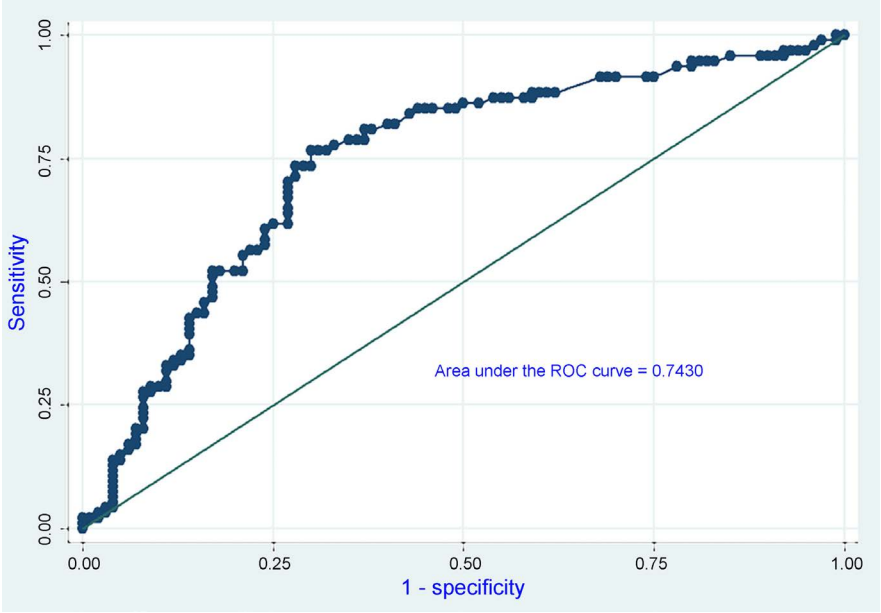

Figure 4. ROC curve of admission glucose for predicting all-cause in-hospital mortality.

value with the highest sensitivity and specificity in predicting 10-day all-cause in-hospital mortality.

Survival was worst in stroke patients with hyperglycemia than those without hyperglycemia. Our finding agrees with that of previous studies that reported hyperglycemia, acute or chronic, to be associated with increased mortality and worse clinical outcomes [1] [2] [3]. In this regard, Masrur *et al.* [1] found that blood glucose > 140 mg/dL (adjusted OR 1.68; 95%CI 1.57 - 1.80) in patients with acute stroke was independently associated with in-hospital mortality. Similarly Marulaiah *et al.* [2] reported a significantly ($p < 0.0001$) higher mortality rates in hyperglycemic than normoglycemic stroke patients.

Hyperglycemic patients with severe stroke had a poor survival than those with mild to moderate stroke. Our finding is consistent with that of previous reports of a major negative impact of initial stroke severity on the likelihood of death following acute stroke [11]. In this regard, Bhaskar *et al.* [12] observed that initial stroke severity (aOR 1.16; 95%CI 1.12 - 1.20) independently predicted mortality following acute ischemic stroke. Similar finding has been also reported by Papagianni *et al.* [13] who found National Institute of Health Stroke Scale (NIHSS) at admission (RR 1.19; 95%CI 1.14 - 1.23; $p < 0.001$) to be one of the main predictors of in-hospital mortality after ischemic stroke. In accordance with the abovementioned studies, Hong *et al.* [14] and Fonarow *et al.* [15] reported the predominance of greater initial stroke severity over all other factors for the worse outcome of acute stroke.

Hyperglycemic stroke patients without known diabetes (stress hyperglycemia) tended to experience a worst survival than those with known diabetes (chronic hyperglycemia) in the present study. Our finding agrees with previous reports by Capes *et al.* [16] and others [3] [17] of a relatively worse prognosis in hypergly-

cemic patients without a prior history of diabetes compared to those with known diabetes. The apparent better survival seen in diabetic patients could be explained by the fact that preconditioning by chronic elevation in blood glucose levels may offset stress-induced sympathetic autonomic nervous system activation and subsequent adverse metabolic effects. Moreover, some medications such as antihypertensive drugs (inhibitors of renin angiotensin system, calcium channel blockers, beta- blockers), statins and antiplatelet drugs that diabetics are frequently prescribed may confer a protective effect against acute stress response [11] [16] [17] [18]. This differential impact of hyperglycemia on outcomes among stroke patients without and with a history of diabetes has been illustrated by Snarska *et al.* [19] who reported a cut-off value of blood glucose concentrations for predicting death of 113.5 mg/dL and 210.5 mg/dL among stroke patients without and with a history of diabetes, respectively.

Nearly half and more than half of deaths occurred in the whole group and the hyperglycemic subgroup, respectively. This observed mortality is somewhat similar to that of 44% and 47% reported ten years ago by Longo-Mbenza *et al.* [20] in the same setting and by Kuate *et al.* [21] at Douala in Cameroon, respectively. However, it is quite higher than that found by most other studies from sub-Saharan African countries [22]-[28]. The differences in the number of deaths between studies and countries could be explained by the differences in public health response against stroke, access to health services, treatment options, population studied, sample size and study design, statistical methods and threshold used to define hyperglycemia [24].

Stroke severity and hyperglycemia were the main predictors of 10-day all-cause in-hospital mortality in the present study. Our finding agrees with that of previous studies from sub-Saharan African countries reporting stroke severity or need of cardio-pulmonary resuscitation and hyperglycemia as main predictors of poor outcomes [20] [27] [28] [29] [30] and adds insights to the relative influence of stroke severity and hyperglycemia on clinical and neurological outcomes following stroke occurrence [31]. Even though most studies have shown that hyperglycemia at admission confers a worse prognosis following acute stroke, it is still unclear whether it only reflects stroke severity or it is directly associated with outcomes [2] [32]. Although some studies have suggested acute hyperglycemia as a marker of stroke severity, the majority of basic science research support the theory that hyperglycemia at admission leads to worsened outcomes through its direct toxic effects on the brain tissue (in particular to the vulnerable ischemic penumbra) possibly because of the accumulation of lactic acid secondary to anaerobic metabolism, enhanced excitatory neurotransmitter (glutamate, aspartate) release, and increased cerebral edema [2] [33]. Hyperglycemia has been also reported to promote oxidative stress, inflammation and neuronal apoptosis, alter cerebral microcirculation with subsequent blood-brain barrier disruption [33] [34] [35]. All these biochemical, molecular and metabolic changes translate into infarct volume growth and hemorrhagic transformation,

decreased recanalization rates, hematoma and peri-hematoma edema size growth, increased risk of poor neurological outcome and mortality [3] [18] [35]. The finding of hyperglycemia as a predictor of mortality independent of stroke severity does suggest that hyperglycemia in the present study could have direct toxic effects on the brain tissue [33]. Despite the lack of randomized evidence on the beneficial effects of insulin therapy in acute stroke, our finding does support recommendations from current guidelines for good glycemic control in patients with acute stroke [36].

Admission blood glucose concentrations had a good predictive performance in predicting 10-day all-cause in-hospital mortality in the present study. The good performance of random blood glucose concentrations in predicting poor outcomes in acute stroke has been already reported. Similar to our finding, Sung *et al.* [3] reported in a study on the predictive performance of various glycemic indices that random blood glucose concentrations (AUC 0.564; 95%CI 0.519 - 0.609; p = 0.026) and fasting plasma glucose (AUC 0.598; 95%CI 0.553 - 0.642; p = 0.001) were significant predictors of poor outcomes in acute ischemic stroke. Similar finding has been reported by Snarska *et al.* [19] who found in hyperglycemic patients with and without a history of diabetes that the area under the curve of admission blood glucose was significantly higher than 0.50 indicating the good predictive value of this parameter for predicting stroke outcome.

We found 154 mg/L as the blood glucose concentration value with the highest sensitivity and specificity in predicting all-cause in-hospital mortality. Similar to our finding, Nardi *et al.* [37] using ROC analysis found blood glucose concentration ≥ 143 mg/dl as the only significant predictive value for 72-hour fatality (sensitivity 88% and specificity 62%), especially in non-diabetics (sensitivity 88% and specificity 62%). In contrast to Nardi *et al.* study, Sung *et al.* [3] reported 127 mg/dL (sensitivity 74.6%, specificity 39.3%) as the value with the highest sensitivity and specificity in predicting outcomes in acute stroke. The differences in optimal blood glucose levels between the studies could be explained by differences in criteria used to define hyperglycemia and to include patients in the study as well as the treatment prescribed to patients. The exact threshold at which elevated blood glucose levels are associated with increased risk of poor outcomes is not yet well established. Thus, the clinical guidelines published by American Heart Association/American Stroke Association and European Stroke Organization recommend that glycemic levels of patients with acute stroke be maintained below 180 mg/dl. This cutoff based on the consensus of Experts does not support maintaining blood glucose concentrations at a specific level improves outcomes [36] [38]. Thus, ROC analysis which enables the comparison of the predictive performance of various glycemic indices and provides information on sensitivity and specificity (not afforded by consensus threshold) could be an alternative in identifying the optimal value of blood glucose for the prediction of outcomes in acute stroke [3].

The interpretation of the results of the present study should take into account

some limitations. First, the small sample size did not allow sufficient power to statistical tests to identify association between variables of interest. Second, single measurement of blood glucose concentration could lead to regression dilution bias and misclassification of patients. Third, the lack of glycated hemoglobin measurements could have underestimated the frequency of chronic hyperglycemia.

6. Conclusion

Admission hyperglycemia with an optimal value of 154 mg/dL for predicting 10-day all-cause mortality emerged in the present study as an independent predictor of in-hospital mortality highlighting thus the need in accordance with guidelines recommendations for a better glucose control to improve acute stroke outcomes.

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Authors Contribution

JKT collected data, participated in data analysis and reviewed the manuscript. FBl conceived the study, participated in data analysis and drafted the manuscript. FPK participated in data analysis and reviewed the manuscript. JRRM participated in statistical analysis of data and reviewed the manuscript. EKS participated in statistical analysis of data and reviewed the manuscript. PZA participated in statistical analysis of data and reviewed the manuscript. ANN participated in statistical analysis of data and reviewed the manuscript. FMM reviewed the manuscript. AIM reviewed the manuscript. SM reviewed the manuscript. EBA reviewed the manuscript. JPMI reviewed the manuscript. WDM reviewed the manuscript. PMM revised the manuscript. AMK participated in study conception and revised the manuscript.

Conflicts of Interest

No conflict.

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