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Blood glucose on admission may predict the mortality of acute intracerebral hemorrhage

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Abstract

Background: Hyperglycemia is a frequent finding in acute intracerebral hemorrhage (ICH), but there is debate concerning its prognostic significance.

Objective: To investigate the impact of blood glucose (BG) measured during admission on short-term mortality and functional outcome in hospital-admitted patients with acute ICH.

Methods: This prospective cohort study included 224 ICH patients [age 60 (50-70) years, median (IQR); female 99 (44.2%)] in the stroke unit of the National Institute of Neurosciences and Hospital Dhaka, Bangladesh from July 2019 to December 2019. All patients underwent routine clinical examination, neuroimaging, and biochemical tests. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Capillary BG was measured using a standardized glucometer. BG level ≥10 mmol/L was used as the cut-off for elevated BG. Mortality was noted and functional assessment was done by modified Rankin Scale (mRS) score at 30 days from ictus.

Result: The NIHSS score, ICH volume, and frequency of aspiration pneumonia were significantly higher whereas the GCS score was significantly lower in the elevated BG group (p=0.002, 0.036, 0.022, and 0.022 respectively). In-hospital mortality, mortality after 30 days, and mRS score after 30 days were also higher in the elevated BG group (p=0.003 in all). Cumulative survival of ICH patients was significantly lower in the elevated BG group after 30-days of acute stroke event (p<0.001). When adjusted for age, creatinine, presence of aspiration, midline shift in CT scan, volume, site, and ventricular extension of ICH, multivariate Cox regression revealed that admission BG could independently predict the mortality 30 days after ICH [HR 1.11 (95%CI 1.06-1.16; p<0.001).

Conclusions: In patients with acute ICH, admission BG is linked to an increase in 30-day and in-hospital mortality rates. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2022; 1 (1): 15-21]*

Keywords: Blood glucose, Acute intracerebral hemorrhage, Mortality

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Introduction

Intracerebral hemorrhage (ICH) is a common stroke subtype that represents a substantial, global, unmet health need with a high mortality and disability rate. The incidence of morbidity and death in ICH has not declined over the past 30 years. Depending on the hemorrhage site, the death rate at one-year ranges from 51% to 65%, and the first two days account for half of all fatalities.[1] However, compared with ischemic stroke, there are still very few effective managements of ICH, despite unceasing attempts.[2]

Diabetes mellitus is a recognized independent risk factor for both ischemic and hemorrhagic stroke. Hyperglycemia is a frequent finding in acute ICH, but there is debate concerning its prognostic significance.[3-5] Hyperglycemia may result in enlargement of hematomas, poor functional recovery, and high mortality following hemorrhagic stroke.[6] Due to concomitant poor glycemic status, patients with diabetes may have high blood sugar at the outset of a stroke. This is not unusual considering that only a small percentage of persons with diabetes globally are able to achieve their hemoglobin A1c (HbA1c) goal.[7] On the other hand, an increase in the levels of counter-regulatory hormones (cortisol, catecholamines, glucagon, etc.) and the accompanying acceleration of gluconeogenesis cause stress-induced hyperglycemia (SIH), which is identified in critical diseases.[8] In addition to DM, SIH may be an important cause of a rise in admission blood glucose (BG). Whether caused by pre-existing DM or SIH, hyperglycemia itself has a detrimental effect on ICH outcomes. Nevertheless, glycemic management goals for hospitalized stroke patients were unknown until recently. In the acute ischemic stroke patient, intensive glycemic management did not significantly differ from the standard of care, according to the SHINE (Stroke Hyperglycemia Insulin Network Effort) trial.[9] But the questions remain for other stroke types including ICH.

To ascertain the glycemic status during the acute event of stroke many investigators have used different methods like measurement of HbA1c, highest BG after admission, mean BG, or glycemic gap calculated from HbA1c and BG. The admission blood glucose remains an excellent indicator of the glycemic status of an acutely ill ICH patient because the glucose-lowering medication is promptly initiated after admission when necessary. The aim of the current study was to investigate whether admission BG was associated with short-term mortalities in patients with acute ICH admitted to a referral neuroscience institute in Bangladesh.

Methods

Study design:

This prospective cohort study was conducted in the stroke unit of the National Institute of Neurosciences and Hospital Dhaka, Bangladesh from July 2019 to December 2019. A total of 345 admitted patients in the stroke unit were screened for inclusion, of which 224 ICH patients were included in the study [Figure-1]. Among those 211 (94.2%) had supra-tentorial and 13 (5.8%) had infra-tentorial hemorrhage. In the supra-tentorial hemorrhage group, the majority were ganglio-thalamic (62.5%) followed by lobar (35.5%) and primary intraventricular hemorrhage (1.5%). On the other hand, in the infra-tentorial hemorrhage group, 53.2% had cerebellar and 46.8% had brain stem hemorrhage.

Clinical variables, neuroimaging, and blood glucose:

Upon admission, all patients underwent routine clinical examination, neuroimaging, and biochemical tests. All data were collected in a structured case record form. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Patients underwent CT scans during the time of admission for screening of hemorrhage. Capillary blood glucose was measured using a standardized glucometer (Accucheck active, Roche). Blood glucose level ≥10 mmol/L was used as

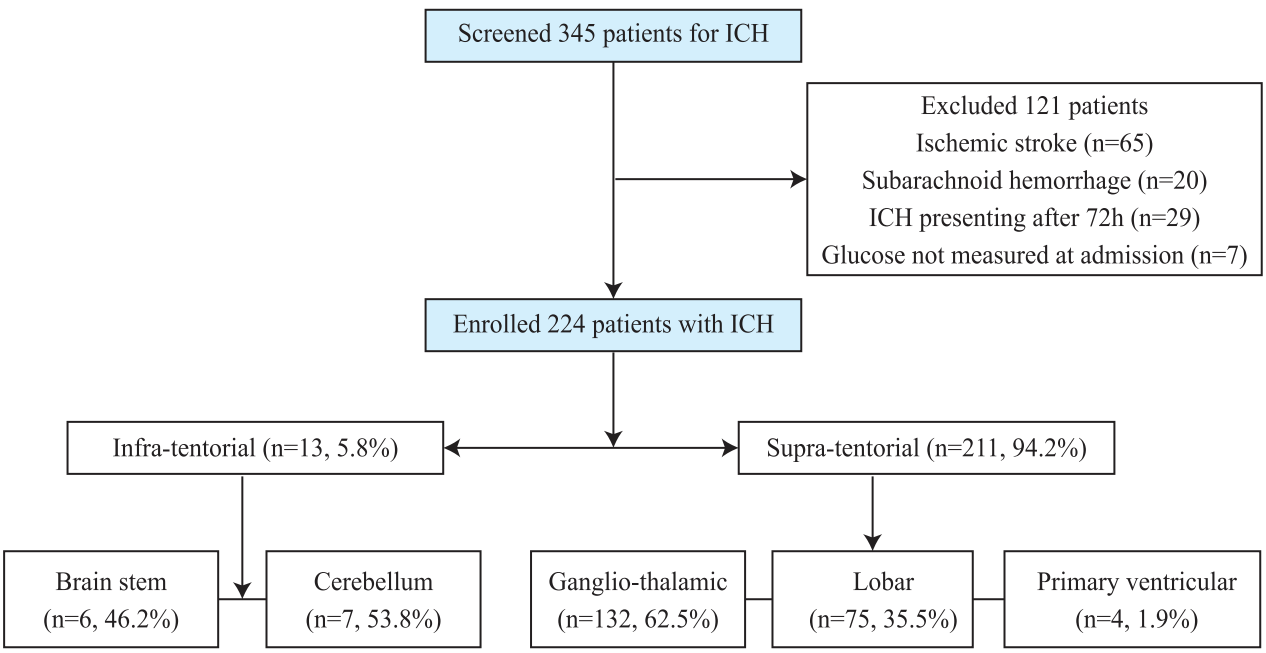

Figure 1: The scheme of enrollment and radiological subtypes of ICH (ICH: Intracerebral hemorrhage)

the cut-off for elevated blood glucose throughout the analysis.

Endpoints and follow-ups:

The modified Rankin Scale (mRS) score during discharge and at 30 days was used as an indicator of functional outcome. All patients were requested to attend for follow-up in the stroke clinic after 30 days from ictus, those who were unable to attend, a functional assessment was done by a telephonic conversation with the patient or their attendant.

Table-I: Demographic and clinical characteristics of the study participants (n=224) assessed at hospital admission

Characteristics		**All participants (n=224)**	**BG <10 mmol/L (n=166)**	**BG ≥10 mmol/L (n=58)**	***p**
Age (years; median and IQR)		60 (50-70)	60.0 (50.0-70.0)	62.5 (54.8-70.0)	0.428
Sex	Male	125 (55.8)	89 (53.6)	36 (62.1)	0.264
	Female	99 (44.2)	77 (46.4)	22 (37.9)	
History of hypertension		161 (71.9)	116 (69.9)	45 (77.6)	0.261
History of diabetes mellitus		34 (15.2)	9 (5.4)	25 (43.1)	<0.001
History of cardiac disease		17 (7.6)	8 (4.8)	9 (15.5)	0.008
Smoking history		68 (30.4)	51 (30.7)	17 (29.3)	0.840
BG (mmol/L, median and IQR)		8.4 (7.1-10.1)	7.8 (6.8-8.6)	11.7 (10.9-14.1)	<0.001
Serum creatinine (mg/dL, median and IQR)		0.91 (0.76-1.66)	0.87 (0.73-1.06)	1.10 (0.83-1.40)	<0.001
Serum sodium (mmol/L, median and IQR)		139 (136-142)	139 (136-142)	138 (136-142)	0.650
Serum potassium (mmol/L, median and IQR)		3.6 (3.3-3.9)	3.6 (3.3-3.8)	3.7 (3.5-4.2)	0.038
GCS score (median and IQR)		9 (7-13)	10 (8-13)	8 (6-11)	0.022
NIHSS score (median and IQR)		20 (14-26)	20 (12-25)	24 (17-30)	0.002
Systolic BP (mm Hg; median and IQR)		160 (140-180)	160 (140-170)	170 (149-183)	0.005
Diastolic BP (mm Hg; median and IQR)		90 (80-100)	90 (80-100)	100 (84-100)	0.241
ICH volume (ml; median and IQR)		24 (10-48)	22 (10-42)	30 (15-77)	0.036
Ventricular extension		123 (54.9)	88 (53.0)	35 (60.3)	0.334
ICH location	Supratentorial	211 (94.2)	156 (94.0)	55 (94.8)	0.811
	Infratentorial	13 (5.8)	10 (6.0)	3 (5.2)	
Midline shift		88 (39.3)	61 (36.7)	27 (46.6)	0.188

Within parentheses are percentages over column total if not mentioned otherwise
*p-value stands for comparison between <10 and ≥10 mmol/L BG group
BG: blood glucose IQR: Interquartile range
GCS: Glasgow Coma Scale NIHSS: National Institutes of Health Stroke Scale
BP: blood pressure CH: Intracerebral hemorrhage

Table-II: In-hospital events and outcome of the study participants (n=224)

Parameters	**All participants**	**BG <10 mmol/L**	**BG ≥10 mmol/L**	***p**
Aspiration	**(n=224)**	**(n=166)**	**(n=58)**	
Surgical measures	47 (21.0)	28 (16.9)	19 (32.8)	0.011
Hospital stay of patients discharged to home (n=158)	8 (3.6)	5 (3.0)	3 (5.2)	0.445
(days; median and IQR)	6 (5-8)	6 (5-7)	7 (5-9)	0.282
In-hospital mortality	70 (31.3)	43 (25.0)	27 (46.6)	0.003
Mortality at 30 days	98 (43.8)	63 (38.0)	35 (60.3)	0.003
mRS score at 30 days	5 (4-6)	5 (3-6)	6 (5-6)	0.003

Within parentheses are percentages over column total if not mentioned otherwise;
*p-value stands for comparison between <10 and ≥10 mmol/L BG group
BG: blood glucose; IQR: Interquartile range; mRS: modified Rankin scale

Statistical analysis:
Quantitative data that did not follow the normal distribution were expressed as a median and interquartile range (IQR). The Mann-Whitney U test was used to compare between two groups. Categorical variables were described using a percentage and the level of significance was measured using the Chi-square test. Kaplan-Meier survival curves were used to analyze the value of the blood glucose level for predicting death and the p-value was determined by using the log-rank test. We used univariate Cox regression to analyze the relationship between different factors and outcomes of an acute ICH at 30 days. Factors with a $p < 0.1$ were re-analyzed using a multivariate Cox-regression model to determine the relationship between admission blood glucose and mortality in ICH. IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.) was used for statistical analysis. A $p<0.05$ was considered a significant difference.

Ethical consideration:
Ethical approval was taken from Institutional Review Board (IRB) for the study. Patients were included in the study after taking prior written consent from his/her legal custodian after being clearly briefed about the nature, purpose, and procedure of the study. Participants' right to refuse to participate or to withdraw from the study was reserved. They were assured of the confidentiality of the information given by them. The study participants were not subjected to any physical or psychological risk. All participants received routine conventional management during their stay in the hospital. Neither any additional invasive nor non-invasive procedures were performed on the participants.

Results

Characteristics of the study participants:
A total of 224 patients (male 125, female 99) admitted with ICH, were enrolled in this study [Table-I]. The median age of the patients was 60 years (IQR, 50–70 years). The majority had a prior history of hypertension (71.9%) whereas only 15.2% had a history of DM. Of the patients with diabetes, 43.1% had elevated blood glucose (≥10 mmol/L) during admission. The frequency of cardiac disease was significantly higher in the elevated blood glucose group (p=0.008), however, the numbers of smokers were not different between the groups (p=0.840). Both median blood glucose and creatinine level were significantly higher in elevated blood glucose group [normal vs. elevated glucose group: blood glucose 7.8 (6.8-8.6) vs 11.7 (10.9-14.1) mmol/L; creatinine 0.87 (0.73-1.06) vs 1.10 (0.83-1.40) mg/dL respectively; p<0.001 for both]. Serum sodium levels were not different (p=0.650) whereas potassium level was higher (p=0.038) in the elevated blood

Table-III: Predictors of prognosis (30-day mortality) of the study participants by univariate and multivariate Cox regression

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, per year increase	1.02 (1.00-1.03)	0.051	1.01 (0.99-1.03)	0.243
Female sex	0.78 (0.52-1.17)	0.235	-	-
Systolic blood pressure, per mm of Hg increase	1.00 (1.00-1.01)	0.279	-	-
Diastolic blood pressure, per mm of Hg increase	1.01 (0.99-1.02)	0.324	-	-
Admission blood glucose, per mmol increase	1.10 (1.06-1.14)	<0.001	1.11 (1.06-1.16)	<0.001
Prior history of hypertension	0.94 (0.61-1.46)	0.795	-	-
Prior history of diabetes	1.25 (0.74-2.11)	0.402	-	-
Serum sodium, per mmol increase	1.01 (0.97-1.04)	0.676	-	-
Serum creatinine, per mg/dl increase	1.15 (0.98-1.35)	0.096	0.90 (0.74-1.10)	0.288
Aspiration	4.60 (3.04-6.95)	<0.001	4.40 (2.82-6.84)	<0.001
ICH volume, per ml increase	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	0.007
Ventricular extension of hemorrhage	1.49 (0.99-2.24)	0.057	1.01 (0.65-1.57)	0.970
Midline shift, per mm increase	2.28 (1.54-3.40)	<0.001	0.63 (0.39-1.02)	0.059
Infratentorial hemorrhage	1.78 (1.03-2.91)	0.040	0.70 (0.21-2.33)	0.565

HR: hazard ratio CI: confidence interval
ICH: Intracerebral hemorrhage

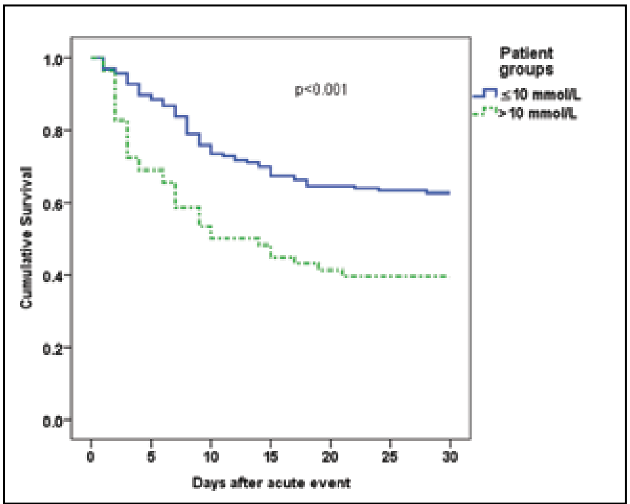

Figure-2: Kaplan-Meier survival curve from day 0 until day 30 showing cumulative survival of ICH patients with or without admission hyperglycemia (≥10 mmol/L) p-value by log-rank test

glucose group. The median NIHSS score at the time of admission was 20 (IQR, 14-26) in all patients and significantly higher in the elevated BG group (p=0.002). Furthermore, the GCS score was significantly lower in the elevated BG group (p=0.022). Median systolic blood pressure was also significantly higher in the elevated BG group (p=0.005), whereas diastolic BP was statistically similar (p=0.241). Significant differences were also found in ICH volume which was higher in elevated BG Group (p=0.036).

In-hospital events and outcomes:

The frequency of aspiration pneumonia was observed to be higher in the elevated blood glucose group (p=0.011), and so were the in-hospital mortality, and mortality after 30 days (p=0.003 for both). Furthermore, the mRS score after 30 days was significantly higher in the elevated BG group (p=0.003) [Table-II]. Kaplan-Meier curve demonstrated that cumulative survival of ICH patients was significantly lower in the elevated BG group after 30-days of acute stroke event (p<0.001) [Figure-2]. Taking the factors with p<0.1 in univariate Cox-regression analysis, multivariate Cox regression showed that admission BG, aspiration pneumonia, and ICH volume could independently predict mortality 30 days after ICH [Table-III]. The hazard ratio (HR) of admission BG was 1.11 (95%CI 1.06-1.16; p<0.001).

Discussion

This prospective cohort study revealed that raised admission BG was associated with an increased risk of mortality in ICH patients at 30-days after the stroke event. An increase in blood glucose by 1 mmol/L during admission was associated with an 11% increased risk of mortality at 30 days. Elevated BG was associated with a higher frequency of cardiac disease, higher NIHSS score, systolic BP, creatinine, potassium, and hematoma volume, but a lower GCS score. The functional outcome assessed by the mRS score was poor and the frequency of aspiration pneumonia, in-hospital mortality, and mortality after 30 days was higher in the elevated BG group.

ICH is one of the devastating neurological emergencies, the outcome of which is poor even in well-developed centers.[1] There are many factors that had been associated with poor outcomes, like early neurological worsening, hematoma enlargement, midline shift, and higher Hemphill ICH score.[10] The Hemphill ICH score components are admission GCS score, initial hematoma volume, presence of intraventricular hemorrhage, infratentorial ICH origin, and age.[11] Although BG is not included in the prognostic scores, in a study carried out in the same center of the current study, Islam et al. suggest that admission BG is a good candidate to be incorporated in those.[12] The correlation between hyperglycemia and neurological prognosis following ICH has a number of plausible reasons. Studies on both humans and animals have shown a link between hyperglycemia and an increase in cerebral edema and perihematomal cell death.[13-14] An increase in blood sugar was linked to a 1.25 relative risk of edema expansion and a >2-fold greater risk of hematoma expansion.[13] Furthermore, hyperglycemia is connected to an increased risk of infection and sepsis.[15] These several elements imposed by increased BG may combine to worsen the prognosis of ICH.

In a number of studies, poor outcome of intracerebral hemorrhage was observed to be associated with 'glycemic gap' which is defined as HbA1c-derived average glucose (28.7×HbA1c-46.7 mg/dL) subtracted from admission glucose.[16,17] The reason behind using glycemic gap was to overcome the effect of premorbid blood glucose control on the admission BG. Although it may be a better measure for stress-induced hyperglycemia, absolute BG values might be more important in stroke pathogenesis. Hence, the present study evaluated admission BG instead of the glycemic gap. Another indicator of poor glycemic status is considered to be the 'highest in-hospital glucose measurement', which is also associated with poor outcomes in ICH.[18] But again highest glucose is governed by different in-hospital management standards. So, admission BG seems to be more suitable for predicting stroke outcomes. We used the cut-off for elevated BG as ≥10 mmol/L, as this is the level beyond which intervention to lower glucose is recommended.[19]

A significant strength of the study is its inclusion of participants regardless of hemorrhage size or location so that the study population is an accurate reflection of the actual patient population encountered in clinical settings. There was no participant drop-out and the sample size was comparatively large. Limitations of the study include unequal group size. As the study center serves as a tertiary referral center, there were inevitable discrepancies among patients in relation to the timing of admission BG measurement as transport times varied depending on geographic and logistic considerations. Long-term outcomes were not evaluated in the study. Lastly, relationships observed in this study do not imply causation, and randomized clinical trials are required to ascertain whether active BG control will result in better outcomes.

Conclusion

In patients with acute ICH, admission BG is linked to an increase in 30-day and in-hospital mortality rates.

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Conflict Of Interest

The authors have no conflicts of interest to disclose

Financial Disclosure

The author(s) received no specific funding for this work.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board. The written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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