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RESEARCH ARTICLE

Admission glycemic gap and other glycemic indices in assessing the need for mechanical ventilation among neurocritical patients with diabetes mellitus

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Abstract

Background: We explored the value of admission glycemic gap (AGG) and other glycemic indices in determining the need for mechanical ventilation (MV) among neurocritical patients with diabetes mellitus.

Methods: We purposively included 60 adult neurocritical patients with diabetes mellitus and prospectively studied them for 30 days, or until discharge or death. These patients stayed in the intensive care unit for at least 24 hours and did not require MV within the first twelve hours of admission. The glycemic indices included admission blood glucose level, A1c (HbA1c) level, A1c-derived admission glucose, A1c level, and AGG. The need for initiation of MV was determined according to standard institutional guidelines.

Results: Among the 60 patients enrolled, 39 (65%) required MV. The need for MV was associated with female gender, ischemic stroke, history of insulin use, higher serum creatinine level, lower mean arterial pressure, higher AGG, admission blood glucose level, A1c, and A1c-derived admission glucose. A per unit rise of AGG (odds ratio (OR) 2.1; 95% confidence interval (CI) 1.4–3.1), and A1c (OR 2.6; 95% CI 1.2–5.4) had significant odds for the need for MV. AGG showed an optimal cut off value of 3.2 mmol/L, with a 79% and 81% sensitivity and specificity, respectively. The area under the curve was 0.79 (95% CI 0.66–0.91) for MV.

Conclusion: Among neurocritical patients with diabetes mellitus, all of the evaluated glycemic indices affect the need for MV. The AGG cut-off of 3.2 mmol/L is an acceptable value to predict the need for MV.

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Key messages

Raised levels of admission glycemic gap, A1c-derived admission glucose, A1c, and admission blood glucose level are associated with a consequent need for mechanical ventilation among neurocritical patients with diabetes mellitus. An admission glycemic gap cut-off of 3.2 mmol/L can be considered acceptable to predict the need for mechanical ventilation.

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Introduction

There is an association between poor hospital outcomes with altered glycemic indices at the time of hospital admission [1–3]. Neurological conditions are among the most common reasons for intensive care unit (ICU) admission. Approximately 10-15% of all ICU patients are severely ill with major neurological or neurosurgical problems affecting the brain and spinal cord that necessitate life-sustaining care and close monitoring [2,4,5]. Most neurocritical patients presenting with at least one co-morbid illness, diabetes mellitus (DM) is the second most prevalent comorbidity after hypertension [6].

In the intensive care unit, among the patients with neurocritical illness, about 20% require mechanical ventilation (MV) [7]. While some patients do not require mechanical breathing right away, may need some MV subsequently [8]. Although the use of MV can be lifesaving, the decision to initiate it must not be a fast approach. Rather, it is advised to use a be made cacetiasly, based on criteria to accurately predict which patients will most likely benefit from these interventions [9,10].

Altered glycemic indices are some of the risk variables linked to unfavorable outcomes in critically ill patients [3,11]. Patients with greater HbA1c (here-in -after denoted as A1c) have increased unfavorable outcomes, including raised mortality rates in the critical care unit [12]. However, chronic hyperglycemia could be associated with cellular mechanisms that buffer against injury induced by acute hyperglycemia amid severe illness [3,13]. Choosing the "optimal glycemic target" is therefore not the only consideration; other dimensions of glycemic management may also be more important. This is why adverse outcomes in critical illness have been linked to glycemic variability, which measures the extent of glycemic excursions during the day [3,14].

In critically ill patients, hyperglycemia may result from stress-induced hyperglycemia (SIH), which can occur with or without diabetes mellitus, or from the patient's preexisting diabetic condition [15]. Since many diabetic patients already have elevated blood glucose levels, the measurement of direct admission blood glucose indices may not be reliably related to stress levels. However, the admission glycemic gap (AGG) has been found to be a more accurate indicator of SIH than the other glycemic indices [16,17]. Other than exploring the relationship with SIH, in critically ill diabetic patients, AGG has also been used to assess the severity of the disease, forecast outcomes, including mortality. An assessment of AGG can minimize the confounding effect of persistent hyperglycemia on the evaluation of the severity of DM [17]. The AGG has been proposed as a predictor of various adverse outcomes in the ICU settings in various scientific works [2,3,11,12,15–17].

In this context, our primary objective was to investigate the role of AGG and other glycemic indices (admission blood glucose, A1c, and ADAG) at ICU admission on clinical outcomes, such as the need for MV in neurocritical patients with DM. Additionally, attempted to determine a cut-off value of glycemic indices, especially of AGG, that can effectively predict the need for MV in the later stage of the same ICU admission. Another specific objective of the work was to evaluate how MV affects some other adverse clinical outcomes, such as survival, development of acute respiratory syndrome (ARDS), multi-organ dysfunction (MODS), and need for renal replacement therapy (RRT) in these patients.

Methods

Design, place, and population

For a duration of 12 months, from October 2022 to October 2023, this prospective observational case study was conducted in the intensive care unit (ICU) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, under the auspices of the Department of Anesthesia, Analgesia, and Critical Care Medicine. The minimum sample size calculated, at 5% acceptable error and 80% power, for this study was 54. Sample size calculation was done using the area under the receiver operating characteristic curve (AUROC) value in the Medcalc software (MedCalc - version 23.1.1). AUROC of AGG for respiratory failure among ICU patients with DM (AUROC= 0.714) in the work of Donagaon and Dharmalingam, 2018 [2], was taken into consideration. However, all of the 60 patients with neurocritical illness who were admitted to the ICU during the stated timeframe and met inclusion criteria were purposively included. All study participants were older than 18 years, had a history of documented DM or an initial post-admission A1c >6.5% (patients who had no history of known DM, yet A1c was >6.5%, included as undiagnosed DM), had survived and spent a minimum of 24 hours in the ICU after admission, and had not required MV within 12 hours of ICU admission. This study excluded individuals who were on corticosteroids, pregnant women, known cases of chronic kidney disease (CKD), those with hemolytic anemia or known hemoglobin variations, hypoglycemic patients, and/or patients who were in hyperglycemic crises during ICU admission.

Data collection, biochemical measurements, and glycemic indices

A pre-tested, semi-structured questionnaire for obtaining data was created. The investigating team came to a consensus before finalizing the data collection instrument. Glasgow coma score, pulse, temperature, blood pressure (BP), mean arterial pressure (MAP), respiratory rate (RR), and partial pressure of oxygen in arterial blood (SpO_2) were among the initial patient assessments that were pertinent to this investigation at the time of admission. The enrolled participants' medical records were reviewed, and notes were made regarding their age, sex, place of residence, primary diagnoses, comorbidities, medication history, and duration of DM. All these variables were considered for this study, as our literature review prior to and during the study showed these as potential factors that affect the need for MV among ICU patients. Within 24 hours of ICU admission, laboratory investigations were sent to the Department of Biochemistry and Molecular Biology, BSMMU, including the arterial blood gas analysis (ABG), complete blood count, A1c (ion-exchange

HPLC method), and serum urea and creatinine, with results noted. The ABG was done using Easy Blood Gas Analyzer (MEDICA, USA), A1c with Abott premium (Hb 9210, USA), blood count with 6 MAX Auto Analyzer (Germany), and serum urea/ creatinine with Diamentian Auto Analyzer (USA).

In the ICU, admission blood glucose level (ABGL) was measured from the capillary blood using a common glucometer (Accu check active, Germany, model 24697034). Before collecting data, glucometer and laboratory oxidase methods were compared in the pre-test, and the variation was less than 0.5 mmol/L. The glucometer reading was confirmed by double-checking a venous sample at the laboratory. The formula used to convert A1c to A1c-derived average glucose (ADAG) at admission was as follows: ADAG (mmol/L) = (1.6 x A1c) − 2.6 [18]. Subtracting the ADAG level from the ABGL allowed for the calculation of the admission glycaemic gap (AGG). As a result, AGG = ADAG - ABGL [16,17].

The participants were all observed for 30 days, or until they were either discharged from ICU or moved to another unit or ward (classified as "survivor") or until death in the ICU (classified as "non-survivor"). The assessment and initiation of MV followed the standard ICU protocol of BSMMU.

Statistical analysis

Continuous data were expressed as mean (standard deviation), and categorical data were expressed as frequencies (percentages). Independent variables were compared between those who needed MV and those who did not. Analyses were performed using the 2-tailed Student's *t*-test for normally distributed continuous variables, or the Mann-Whitney U test for skewed data, and the Chi-square test or Fisher's exact test for categorical variables as appropriate. A logistic regression analysis was performed on those independent variables found statistically significant in the above analysis. Predictor variables were entered as continuous variables, except RRT, which had a binary category and coded '0' for no and '1' for yes response. Receiver operating characteristic (ROC) curves were plotted to analyze the discernibility of the predictive indices, and the area under the curve (AUC) and its 95% confidence interval (CI) were calculated to quantify the discriminative ability of AGG in predicting these outcomes. Youden's index was used to calculate the best possible cut-off values of the glycemic gap, which can predict adverse outcomes. Data were analysed using STATA MP Version 16. A significance α level of 0.05 was used for statistical testing.

Table 1 Baseline characteristics of neurocritical patients with diabetes mellitus based on the need for mechanical ventilation (MV)

Characteristics	Total	Need for MV		*P*
	(n=60)	No (n=21)	Yes (n=39)	
Age (years) mean (SD)	57.7 (2.0)	62.5 (2.5)	55.3 (2.6)	0.07
Age group				
<60 years	27 (45.0)	7 (33.3)	20 (51.3)	0.18
≥60 years	33 (55.0)	14 (66.7)	19 (48.7)	
Sex				
Female	22 (36.8)	12 (57.1)	10 (25.6)	0.02
Male	38 (63.3)	9 (42.9)	29 (74.4)	
Residence				
Rural	33 (55.0)	13 (61.9)	20 (51.3)	0.43
Urban	27 (45.0)	8 (38.1)	19 (48.7)	
Primary diagnosis				
Ischemic stroke	21 (35.0)	11 (52.4)	10 (25.6)	0.04
Traumatic brain injury	13 (21.7)	2 (9.5)	11 (28.2)	0.11
Hemorrhagic stroke	12 (20.0)	3 (14.3)	9 (23.1)	0.51
Others[a]	14 (23.3)	5 (23.8)	9 (23.1)	0.95
Co-morbidities				
Hypertension	39 (65.0)	15 (71.4)	24 (61.5)	0.44
Asthma/COPD	8 (13.3)	3 (14.3)	5 (12.8)	0.99
Ischemic heart disease	4 (6.7)	1 (4.8)	3 (7.7)	0.99
Drug history				
Anti-hypertensive	35 (58.3)	13 (61.9)	22 (56.4)	0.68
Insulin	25 (41.7)	5 (23.8)	20 (51.3)	0.04
Oral anti-diabetic	33 (55.0)	14 (66.7)	19 (48.7)	0.18
Oral anticoagulant	4 (6.7)	2 (9.2)	2 (5.13)	0.61

Results are in number (%), unless indicated otherwise. COPD indicates chronic obstructive pulmonary disease; SD, standard deviation.
[a]Subarachnoid hemorrhage, Guillain Barre Syndrome, motor neuron disease, and meningoencephalitis.

Ethics

The patients/ their consenting guardians were given an easy-to-understand explanation in the local language of the study's goals, risks, and advantages. Every participant/ their guardian was given the assurance that their treatment would not be hampered if they chose not to participate in the research or if they chose to withdraw at any point. Additionally, they received assurances that all information would be kept private and used only for the study.

Results

Overall population

Sixty ICU-admitted patients were included in the study, with a mean age (standard deviation) of 57.7 (2.0) years, and about half of them were from the 60 or more years' age group. The majority (63.3%) of the patients were male, and more than half (55.0%) were from rural residences. Ischemic stroke (35.0%), traumatic brain injury (21.7%), and hemorrhagic stroke (20.0%) were the prevalent diagnoses. Hypertension (65.0%) was the commonest comorbid condition.

Effect of primary and baseline features on MV

Baseline characteristics of patients were classified based on the provision of invasive MV. Among the 60 patients, 39 (65.0%) required MV. A significantly greater number of patients who were on MV were male and receiving insulin treatment **(Table 1)**.

Clinical and laboratory variables

Among the clinical and laboratory findings, MAP was significantly lower in ventilated patients, while ABGL, A1c, ADAG, and serum creatinine were significantly higher in those patients. AGG of mechanically ventilated patients (4.9 (1.8) mmol/L) was considerably higher (P <0.01) than that of non-ventilated patients (2.8 (1.5) mmol/L) **(Table 2)**.

Adverse clinical outcomes associated with MV

The number of patients who developed MODS was higher among the mechanically ventilated patients (P 0.03). Mechanically ventilated patients' survival rates were found to be significantly lower (P =0.01) than those who did not require MV **(Table 3)**.

Effect of AGG and other glycemic indices

Variables related to the primary outcome (MV) were screened out during univariate analysis. The logistic regression analysis revealed the statistically

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Table 2 Clinical and laboratory findings of neurocritical patients with diabetes mellitus according to the need for mechanical ventilation (MV)

Characteristics	Total	Need for MV		*P*
		No	Yes	
	(n=60)	(n=21)	(n=39)	
Clinical Findings				
Pulse (beats/min)	91.4 (16.3)	90.1 (16.5)	92.0 (16.3)	0.67
Temperature				
<100.4⁰ F	49 (81.7)	19 (90.1)	30 (76.9)	0.20
≥100.4⁰ F	11 (18.3)	2 (9.5)	9 (23.1)	
Oedema	2 (3.3)	1 (4.8)	1 (2.6)	0.65
Glasgow coma score[a]	8 (5.5–11.0)	11 (6.0–14.0)	7 (5.0–10.0)	0.07
Respiratory rate (breaths/min)[a]	20 (18.0–22.0)	20 (16.0–20.0)	20 (18.0–22.0)	0.24
Laboratory findings				
MAP (mmHg)	92.1 (14.7)	98.4 (13.6)	88.7 (14.3)	0.01
Oxygen saturation[a]	97 (95.5–98.0)	97 (95.0–98.0)	97 (96.0–99.0)	0.78
PaO_2: FiO_2 ratio	263.9 (227.1)	288.4 (128.1)	250.7 (149.9)	0.33
ABGL (mmol/L)	13.6 (2.9)	11.4 (2.3)	14.7 (2.6)	<0.01
A1c (%)[a]	7.3 (6.9–8.1)	7 (6.6–7.2)	7.8 (7.0–8.2)	<0.01
ADAG (mmol/L)[a]	9 (8.4–10.3)	8.5 (7.9–8.9)	9.8 (8.5–10.4)	<0.01
AGG (mmol/L)	4.16 (1.9)	2.8 (1.5)	4.9 (1.8)	<0.01
Haemoglobin (g/dL)	11.7 (1.3)	11.6 (1.3)	11.7 (1.3)	0.98
WBC count (x10⁹/L)	13.3 (4.0)	12.3 (3.5)	13.8 (4.2)	0.16
Platelet count (x10⁹/L)[a]	210 (170.0–250.0)	210 (165.0–250.0)	210 (170.0–300.0)	0.52
pH[a]	7.5 (7.4–7.5)	7.5 (7.4–7.5)	7.5 (7.4–7.5)	0.90
Serum urea (mg/dL)[a]	39 (28.0–68.4)	35 (26.0–62.0)	40 (30.0–77.0)	0.59
Serum creatinine (mg/dL)[a]	1.0 (0.9–1.8)	0.9 (0.7–1.2)	1.0 (0.9–4.4)	<0.01

MAP, mean arterial pressure; ABGL, admission blood glucose level; ADAG, A1c derived average glucose; AGG, admission glycemic gap; TC, total count; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; WBC, white blood cells
[a]Median (interquartile range), others are mean (standard deviation)

significant association of ABGL, A1c, ADAG, and AGG with MV. One unit increase in the variable was associated with a 2.1 times (95% CI 1.4–3.1) higher requirement for MV (*P* <0.01). An increase of 1 mmol/L ADAG was associated with an 81% increase in the requirement for MV. Elevation of all four glycaemic indices (ABGL, A1c, ADAG, and AGG) significantly increased the risk of MV in neurocritical ICU patients with DM. A1c showed the greatest risk (OR 2.6; 95% CI 1.2–5.4) **(Table 4)**.

Among the glycemic predictors evaluated, the AGG demonstrated good diagnostic performance with a Youden Index of 0.60, which indicates a moderate to good range for predictive performance, at a cut-off value of 3.2 mmol/L. This reflects a good overall sensitivity (79%) and specificity (81%), indicating its potential utility in predicting the requirement for invasive MV. The optimal cut-off value of the AGG was 3.2 mmol/L, with a maximum AUROC of 0.79 (95% CI 0.65–0.91) for MV **(Figure 1 and Table 5)**.

Table 3 Association of adverse clinical outcomes of diabetic neurocritical patients with mechanical ventilation (MV), n (%)

Clinical outcomes	All patients	Need for MV		*P*
		No	Yes	
	(n=60)	(n=21)	(n=39)	
Needed renal replacement therapy	13 (21.7)	2 (9.5)	11 (28.2)	0.11
Developed acute respiratory distress syndrome	19 (31.7)	4 (19.1)	15 (38.5)	0.15
Developed multiple organ dysfunction syndrome	30 (50.0)	5 (23.8)	25 (64.1)	0.03
Survival	25 (41.7)	15 (71.4)	10 (25.6)	0.01

Discussion

This study showed that 65% of neurocritical patients with DM needed MV in the ICU. The majority of our patients were elderly (>60 years) males. Male gender, ischemic stroke, and history of insulin were associated with the need for MV. Per unit raise of all glycemic indices significantly raised the risk of MV. An AGG cut-off value of 3.2 had an AUROC of 0.79 in the case of MV.

Table 4 Logistic regression analysis of the association between glycemic indices with mechanical ventilation (MV)

Predictors	OR (95% CI)
Admission blood glucose level (mmol/L)	1.8 (1.3–2.5)
Hemoglobin A1C (%)	2.6 (1.2–5.4)
A1C-derived admission glucose (mmol/L)	1.8 (1.1–2.9)
Admission glycemic gap (mmol/L)	2.1 (1.4–3.1)
Renal replacement therapy	3.7 (0.7–18.8)

All predictor variables were continuous except for renal replacement therapy, which was a binary category (coded '0' for no and '1' for yes).
OR indicates odds ratio; CI, confidence interval

Evidence that altered glycemic indices at admission may be associated with major therapeutic events like the need for MV in neurocritical patients with DM in the ICU has scarcely been evaluated. Admission glycemic indices in these patients potentially affect the need for MV, and a probable cut-off to predict such an event can be of importance. As such, the predictors and cut-off values will essentially enable the clinician to identify, increase monitoring, and improve management of the most vulnerable patients in ICU setting.

The proportion of patients who needed MV in this study was very high, as other reports suggest that approximately 20% of the neurocritical patients in the ICU need MV [7]. The characteristics of our study population, study design, and study settings may be responsible for the much higher proportion of MV. We selected a study sample of patients who had at least one comorbid condition in addition to their neurological illness, such as DM, neurocritical patients in the general ICU rather than a dedicated ICU, and a 30-day-long observation duration, all of which might have contributed to the high rate of MV. The older patient pool of this study corresponds with Chentli, Azzoug, and Mahgoun [19], who explained that older patients with diabetes mellitus are at higher risk of morbidity and mortality through hyperglycemia-induced damage. Similarly, our sample being male-predominant mirrors the scientific conclusion that males are more likely victims of neuro-critical conditions [6,20,21].

Our finding associating ischemic stroke, CKD, history of insulin use, and male gender with MV is in line with the finding that neurological failure is a proven hazard that necessitates MV [22], that lung inflammation is modulated by insulin [23], and that men are more likely to need MV support [24].

Acute-stress hyperglycemia is indicated by the glycemic gap, and patients with significant glycemic gaps have been shown to have higher mortality rates [25]. Hence we examined whether AGG can influence the requirement for MV and we discovered that AGG, ABGL, ADAG, and A1c all have the potential of predicting the need for MV in neurocritical patients

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Table 5 Receiver operating characteristic curve and Youden index values of glycemic indices for prediction of mechanical ventilation

Predictors	Youden Index	Cut-off values	Sensitivity	Specificity	AUC (95% CI)
Admission blood glucose level (mmol/L)	0.63	>12.2	0.87	0.76	0.84 (0.72–0.96)
Hemoglobin A1C (%)	0.47	>7.4	0.62	0.86	0.75 (0.61–0.88)
A1C-derived admission glucose (mmol/L)	0.47	>9.1	0.62	0.86	0.75 (0.61–0.88)
Admission glycemic gap (mmol/L)	0.60	>3.2	0.79	0.81	0.79 (0.66–0.91)

AUC indicates area under the curve; CI, confidence interval

with DM. All these are in line with the report that hyperglycemia, glycemic gap, and glycemic variability affect and raise the possibility of requiring MV [3]. This may be due to the pathophysiological aspect that hyperglycemia is associated with diaphragmatic dysfunction and respiratory muscle weakness [26,27]. This study's finding of an increase in A1c showing the greatest odds of MV is interesting considering that elevated A1c showed the highest odds of MV in COVID -19 patients [28], was associated with ICU admission after surgery [29], and prolonged ICU stay after bypass graft in the coronary artery [30], etc.

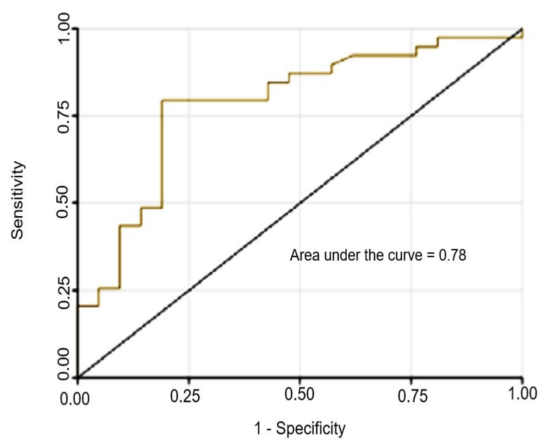

Figure 1 Receiver operating characteristic curve of admission glycemic gap to predict the need for mechanical ventilation

There are some limitations of this study. The sample size was modest, purposively selected, and carried out in a single general intensive care unit. Selection bias is, therefore, possible. Post-surgical neuro-critical patients did not participate in this investigation in large numbers, mostly because the ICU was not designed with post-surgical neurocritical patients in mind. A capillary sample was used to measure the first glucose level, which can vary from a venous sample. Therefore, our findings may not be generalized.

Conclusion

Findings from this study suggest that admission glucose level, A1c level, A1c-derived admission glucose, and AGG can predict the need for MV among the neurocritical patients with DM in the ICU. An AGG >3.2 mmol/L may be considered a marker to predict the need for MV in the defined patient pool.

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Author contributions

Conception and design: MKMa, KTM, MKMo, MA. *Acquisition, analysis, and interpretation of data:* MKMa, KTM, MKMo, MAH, AKMH, MA. *Manuscript drafting and revising it critically:* MKMa, KTM, MKMo, MAH, AKMH, MA. *Approval of the final version of the manuscript:* MKMa, KTM, MKMo, MAH, AKMH, MA. *Guarantor of accuracy and integrity of the work:* MKMa, KTM, MKMo, MA.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

Supplementary file

None

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