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Association of glycosylated hemoglobin with mortality of patients in intensive care unit: a prospective observation study.

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ABSTRACT

INTRODUCTION: Glycated hemoglobin (HbA1c) is the most commonly used clinical test to estimate mean blood glucose during the past 2 to 3 months. In addition to diagnostic purposes, the HbA1c level also predicts diabetes complications. The aim of this study was to determine the association of glycosylated hemoglobin with mortality in intensive care unit (ICU).

MATERIALS AND METHODS: A prospective observational study was conducted in the ICU with a total of 281 patients. These patients were classified into two groups based on their HbA1c levels: one group with HbA1c level < 6.5 % and another group with HbA1c level ≥ 6.5%. The following data were collected during the study period. Clinical details and scores such as the APACHE II score (Acute Physiology and Chronic Health Assessment) and daily SOFA (Sequential Organ Failure Assessment) scores for the period of stay in the ICU. ICU morbidities as the need for mechanical ventilation, the use of inotropes / vasopressors, the length of stay in the ICU, and the requirement of renal replacement therapy (RRT). The outcome measures were ICU mortality and 28-day mortality.

RESULTS: Of 281 patients admitted to the ICU for more than 48 hours, 157 patients (55.9%) had HbA1c levels < 6.5%, with the remaining 124 (44.1%) had levels ≥ 6.5%. ICU mortality was present in 107 (38.07%) cases. ICU mortality was higher in patients in the HbA1c ≥ 6.5% group compared to the HbA1c < 6.5% group. This was statistically significant (p-value <0.001). Mortality at 28 days was observed in 125 (44.48%) cases. Patients with an HbA1c value ≥ 6.5%, there was a higher mortality at 28 days compared to patients with an HbA1c value < 6.5%. This was found to be statistically significant (p-value <0.001).

CONCLUSIONS: The study showed that glycated hemoglobin levels (HbA1c) levels ≥ 6.5% had a significantly higher mortality rate compared to the patient in the HbA1c level < 6.5%.

KEY WORDS: Glycated hemoglobin, intensive care unit, mortality.

INTRODUCTION

Glycated hemoglobin (HbA1c), the commonly used clinical test to estimate mean blood glucose levels, offers a reliable indication of glycaemic control over the past 2 to 3 months. This correlation makes it a valuable tool for diagnosing diabetes and evaluating the effectiveness of treatment [1]. New red blood cells contain less glucose-bound hemoglobin when entering the circulation. A brief increase in blood glucose levels can cause nonenzymatic synthesis of aldimines, which proportional to glucose concentration [2]. Apart from diagnostic purposes, the HbA1c level also predicts diabetes complications because it reflects the more harmful glycation sequelae of diabetes, such as microvascular and macrovascular complications [3].

Hyperglycaemia is the most common metabolic abnormality in critically ill patients. This correctable abnormality is associated with an increased risk of mortality [4]. This hyperglycemia is mainly due to stress-induced hyperglycemia (new-onset hyperglycemia) or chronic hyperglycemia in known diabetic or undiagnosed diabetic patients. New stress-induced hyperglycemia stems from the metabolic reaction to acute illness, characterised by elevated levels of counter-regulatory hormones, causing insulin resistance and decreased insulin secretion. This causes elevated blood sugar levels [5]. HbA1c measurement in critically ill patients helps distinguish patients with stress hyperglycemia from those with undiagnosed diabetic patients or known diabetic patients. Recent acute changes in blood glucose levels, which are often observed in critical illness, did not affect HbA1c [6]. Hence, HbA1c is a more appropriate measure of chronic glycaemic status in intensive care unit (ICU).

Glycosylated hemoglobin is an established indicator of long-term glycaemic control in diabetic patients. In some studies, the impact of high HbA1c levels on mortality has been reported. It has been associated with unfavourable outcomes in acute coronary care and acute medical care settings [7], in perioperative patients, especially coronary artery bypass graft surgeries [8] and in gastric surgery patients [9]. It may be a useful predictor in evaluating the severity of the disease in emergency department (ED) patients in terms of length of stay and ICU referral, reflecting higher healthcare utilization [10].

In critically ill patients, HbA1c is correlated with the severity and clinical outcomes [11,12]. Although some studies showed an association between HbA1c and morbidity and mortality, only a limited number of prospective studies were conducted in critically ill patients. Until now, there has been no clear evidence of an association between the HbA1c level and the prognosis of the ICU, and no clear cut-off HbA1c level for critically ill patients to predict the outcome. Therefore, it is important to know if the preadmission diabetic status influences intensive care unit (ICU). Despite improvements in healthcare technology, mortality and morbidity rates for those with critical diseases remain high. Early identification and control of some of the risk factors can contribute to improved outcomes. Therefore, this study was conducted to determine the association between HbA1c admission and mortality in critically ill patients.

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MATERIALS AND METHODS

The prospective observational study was conducted after approval from the institutional ethics committee (IEC/ABVIMS/RMLH/599) and registering with the clinical trial registry of India (CTRI/2021/12/038525). All patients with an age greater than 18 years and a stay in the intensive care unit stay > 48 hours were included in the study. Consent refusal, patients with chronic kidney disease, pregnant and lactating mothers, patients with jaundice, severe anemia, chronic liver disease and a history of hemoglobinopathies, terminally ill cancer patients, resuscitated patients after cardiac arrest and patients received multiple blood transfusions were excluded.

The sample size for the current study was calculated considering the reference study by Kompoti M et al. [13] considering the crude mortality rate of 20.3% and the power of 95% confidence level of 95% and 80% with a precision of 5%. However, we studied all patients admitted to the ICU during the 1 year. Informed consent was obtained from all patients or relative before being included in the study. The following data were collected during the study period. Demographic data such as age, sex, body mass index (BMI), comorbidities, and admission category. Clinical details and scores such as the APACHE II score and daily SOFA scores for the period of stay in the ICU. ICU morbidities as the need for mechanical ventilation, the use of inotropes / vasopressors, the length of stay in the ICU, and the requirement of renal replacement therapy (RRT). Outcomes in the ICU are discharge or mortality and 28-day mortality.

Blood samples for HbA1c were drawn within the first 24 hours after admission to the ICU. Patients were divided into two groups (HbA1c < 6.5 % and HbA1c <6.5%) for comparison based on the value of HbA1c; a cut-off value of 6.5% was taken according to the diabetic range of the American Diabetes Association. Additionally, we studied the correlations between mortality in two groups. Blood sugar measurements will be taken in all patients and recommend glycemic control in order to maintain the blood sugar level between 140 and 180 mg / dl using intravenous insulin. HbA1c levels were reported using the principles of ion exchange high performance liquid chromatography (HPLC) on the BIO-RAD variant D10^{TM} (Germany). This method has been certified by the National Glycohemoglobin Standardisation Program (NGSP).

The primary objective was to study the association of glycosylated hemoglobin with mortality of the patients in the adult intensive care unit. Secondary objectives were to study the association of glycosylated hemoglobin with morbidity in the ICU, including duration of mechanical ventilation, use of inotropes and vasopressors, length of stay in the requirement of renal replacement therapy, and mortality at 28 days. The data were entered into MS Excel. Data analysis was done using SPSS version 25.0. All continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile ranges), and all categorical variables were expressed as percentages. After evaluation, qualitative data were analyzed using the Chi-square test and the quantitative data were analysed using the independent t-test or Mann–Whitney U test to find the relationship between various parameters and the level of HbA1c. The level of significance was assumed to be < 5% i.e., p-value < 0.05.

RESULTS

The study cohort comprised 856 patients, including medical and surgical cases as well as direct admissions or transfers to a multidisciplinary ICU. 575 patients were excluded from the study according to the exclusion criteria. The main reason for exclusion was not being in the ICU for more than 48 hours. In our study, only 281 patients were considered as a study group for analysis (Figure 1).

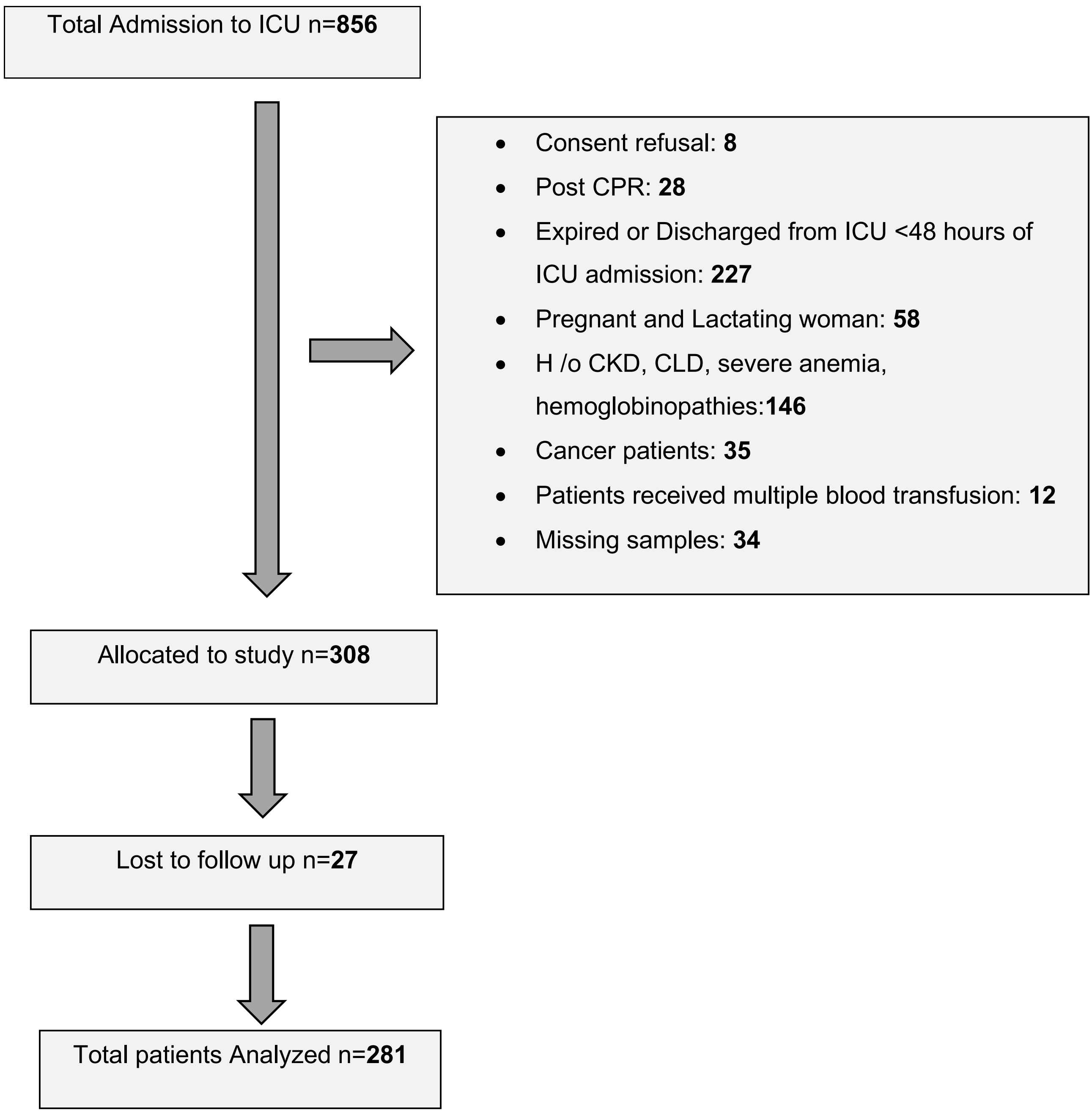

Figure 1. Consort diagram.

Of 281 patients admitted to the ICU for > 48 hours, patients with a HbA1c level of < 6.5% were 157 (55.9%), and patients with an HbA1c level of ≥ 6.5% were 124 (44.1%) (Table 1).

Table 1. Distribution of cases according to HbA1c level.

HbA1c level	Number of cases	Percentage (%)
HbA1c < 6.5%	157	55.9
HbA1c ≥ 6.5%	124	44.1

Among the various comorbidities, patients in the HbA1c 6.5% group had a higher incidence of comorbidities. In these, diabetes mellitus, heart disease, and pulmonary diseases were significantly associated with a high HbA1c level. This was statistically significant. Co-morbidities such as hypertension and thyroid disorders were not statistically significant associations with HbA1c (Table 2).

Table 2. Distribution of cases according to admission category and HbA1c level.

Comorbidity present	HbA1c < 6.5%	HbA1c ≥ 6.5%	p-value
Hypertension	41	44	0.090
Diabetes mellitus	1	90	**<0.001***
Cardiac disease	13	22	**0.017***
Pulmonary disease	40	18	**0.024***
Thyroid disorder	18	18	0.447

*The Chi-square test used: * p-value < 0.05 Significant.*

The mean [standard deviation (SD)] age of the patient (in years), the mean value (SD) of the admission APACHE II score and mean (SD) SOFA score were higher in the population with a value of ≥ 6.5%, and they were statistically significant. The mean BMI (SD) of the patients (In Kg/sqm) were higher in the population with a HbA1c value of ≥6.5%. But it was not statistically significant (p-value 0.316) (Table 3). When comparing HbA1c levels according to clinical outcome, the mean value of HbA1c (SD) that required mechanical ventilation was 6.88 (1.99), the mean (SD) HbA1c value that required RRT was 7.38 (2.40) and the mean HbA1c that required vasopressors or inotropes was 7.02 (2.21). These values were within the diabetic range of < 6.5%. These values were statistically significant. The mean value of HbA1c (%) for more than one week of ICU was 6.83 (2.00), which was higher compared to the mean HbA1c value for less than one week of ICU stay. But it was not statistically significant. (p-value 0.508) (Table 4).

Table 3. Comparison of age, BMI, APACHE and SOFA scores according to the HbA1c level.

	Mean (SD)		p-value
	HbA1c < 6.5%	HbA1c ≥ 6.5%	
Age of the patient (In years)	52.14 (13.10)	56.23 (10.03)	**0.040***
BMI of the patient (In Kg/sqm)	23.82 (3.32)	24.24 (3.58)	0.316
APACHE II score at admission	9.47 (5.49)	11.29 (6.17)	**0.010***
SOFA score (Mean)	3.23 (2.79)	4.25 (3.04)	**0.004***

*The independent t-test used: * p-value < 0.05 Significant.*

Table 4. Comparison of HbA1c levels according to clinical outcome.

Clinical outcome	Needed/Not needed	HbA1c levels Mean (SD)	p-value
Use of mechanical ventilation	Needed	6.88 (1.99)	0.023*
	Not needed	6.22 (1.45)	
Requirement of RRT	Needed	7.38 (2.40)	0.032*
	Not needed	6.66 (1.82)	
Use of inotropes/vasopressors	Needed	7.02 (2.21)	0.007*
	Not needed	6.39 (1.36)	
Duration of ICU stay	Less than one week	6.67 (1.83)	0.508
	More than one week	6.83 (2.00)	

*The independent t-test was used. * p-value < 0.05 Significant.*

In the study population, mortality from the ICU was present in 107 (out of a total of 281) cases (38.07%). ICU mortality was higher in patients in the HbA1c ≥ 6.5% group compared to the HbA1c < 6.5% group. This was statistically significant. 28-day mortality was observed in 125 (of a total of 281) cases, which was 44.48%. In patients with an HbA1c value ≥ 6.5%, there was a higher 28-day mortality at 28 days compared to cases with an HbA1c value < 6.5%. This was found to be statistically significant (Table 5).

Table 5. Distribution of cases according to ICU mortality,, 28-day mortality and HbA1c level.

Mortality		HbA1c < 6.5%	HbA1c ≥ 6.5%	p-value
ICU Mortality	Present	41	66	<0.001*
	Absent	116	58	
28-day Mortality	Present	49	76	<0.001*
	Absent	108	48	

*The chi-square test was used. * p-value < 0.05 Significant.*

DISCUSSION

In this study, HbA1c levels in all the patients admitted to the ICU under the critical care medicine of a tertiary care hospital. In a study by Alghamdi AS et al. [14] it was reported that there was a positive correlation between age and HbA1c levels. According to this study, as age increases, HbA1c levels are also found to increase. The mean age was higher in the population with HbA1c ≥ 6.5% (56.23 ± 10.03 years) as compared to the participants with HbA1c < 6.5% (52.14 ± 13.10 years). This was statistically significant (p-value < 0.040) and similar results were found in previous studies [15,16]. The prevalence of diabetes increased significantly in elderly patients. Several factors may have contributed to this age-related increase in HbA1c levels. Muscle mass decreases with age, which can affect the ability to metabolise glucose. Blood sugar levels may increase as a result of increased insulin resistance. These factors can lead to higher blood glucose levels with age, and, as a consequence, HbA1c also rises [2].

Podder V et al. [17] reported that the prevalence of comorbidities was higher in patients with diabetes. Other studies [13,16] also reported a high number of co-morbidities in patients with high levels of HbA1c. In this study, diabetes mellitus, pulmonary disease, and cardiac disease were significantly associated with a high HbA1c level. We excluded patients with comorbidities that influence the HbA1c value, such as chronic kidney disease and chronic liver disease. HbA1c levels in CKD will be unusually high due to decreased clearance of HbA1c from the blood and increased glycation. In CLD, there will be abnormally low levels of HbA1c due to decreased red blood cells and decreased production of HbA1c. This can result in an underestimation of blood glucose control in patients with CLD [2].

Lionel KR et al. [12] also reported that patients with high HbA1c values had higher admission APACHE II scores. Similar observations were seen in a study by Kompoti M et al. [13]. Farah R et al. [16] also showed that those with higher HbA1c values had a higher APACHE II score compared to those with normal HbA1c. In this study, the mean APACHE II score at admission was higher (11.29 ± 6.17) in the population with an HbA1c value of 6.5% compared to the HbA1c < 6.5 group (9.47 ± 5.49). This was statistically significant (p-value = 0.010). In this study, the mean SOFA score was higher in the population with a HbA1c value of ≥ 6.5% compared to the HbA1c < 6.5% group and it was statistically significant. Mahmoodpoor A et al. [15] and Gornik I et al. [11] also reported that nonsurvivors had higher SOFA scores compared to survivors.

In this study, the overall mortality from the ICU was 38.07%. ICU mortality was higher in patients in the HbA1c ≥ 6.5% group compared to the HbA1c < 6.5% group. This was statistically significant. Lee YS et al. [18] also reported that patients with a HbA1c level ≥ 6.5% at ICU admission were associated with the progression of significant organ dysfunction at 72 hours and ICU mortality. But it was a retrospective observational study and was performed in patients with sepsis only. But in this study, the population was mixed medical and surgical patients and HbA1c ≥ 6.5% showed a significant association with mortality. In our study population, the mean value of HbA1c was noted to be higher in the mortality group (7.5 ± 2.31%) than in the ICU discharge group (6.15 ± 1.23%) group. These results correlate well with the previous prospective studies by Gornik I et al. [11], and Mahmoodpoor A et al. [15]. The study by Gornik et al. [11] was carried out only in septic diabetic patients. The median value of HbA1c was 9.75% higher in non-survivors. Whereas in Mahmoodpoor A et al. [15] study population subjects were surgical ICU patients. The mean value of HbA1c was 7.25±1.8 % significantly higher in non-survivors.

Kompoti M. et al. [13] reported that the duration of mechanical ventilation was longer in pateints with high HbA1c levels. In this study, according to the use of mechanical ventilation and the HbA1c level, a higher number of patients in the HbA1c 6.5% group required mechanical ventilation. Significant association between the use of mechanical ventilation and HbA1c. Lee YS et al. [18] reported that high HbA1c values were associated with severe organ dysfunction and high vasopressor requirement in diabetic patients with sepsis. In this study, a similar high vasopressor requirement in diabetic patients with a higher HbA1c value.

In this study, the mean HbA1c value (%) that required RRT was 7.38 + 2.4%. Between the two groups, the high HbA1c 6.5% group had a higher percentage of the requirement for RRT. Mahmoodpoor A et al. [15] reported an association between high HbA1c values and the incidence of acute kidney injury. Lee YS et al. [18] in a retrospective study reported that patients with a HbA1c level ≥ 6.5% exhibited significant kidney dysfunction 72 hours after ICU admission compared with those with an HbA1c level < 6.5%. This finding was explained by the possibility that a chronic hyperglycemic state can damage the endothelial glycocalyx; This is considered to be the primary mechanism responsible for vascular complications in patients with diabetes mellitus. Kompoti M et al. [13] in a prospective study reported that 13% of the total population required RRT, and this requirement was higher in patients with high HbA1c levels. The findings of this study were similar to those of these studies.

In this study, patients with an HbA1c value ≥ 6.5%, there was a higher mortality at 28 days compared to cases with an HbA1c value < 6.5%. These findings were similar to the study by Farah R et al. [16]. They observed that 30-day all-cause mortality was significantly higher in patients with high levels of HbA1c (≥6%) levels. The study limitations include a small sample size and short duration, as well as recruitment from only one tertiary care hospital. The enhancement of the precision and generalisability of the results would involve recruiting participants from multiple tertiary care hospitals. In addition, future studies with larger sample sizes and longer durations are necessary to ensure more robust findings.

CONCLUSIONS

The study showed that glycated hemoglobin levels (HbA1c) levels ≥ 6.5% had a significantly higher mortality rate compared to the patient in the HbA1c level < 6.5%. The HbA1c level can continue to be used as a diagnostic and predictive tool due to the rising prevalence of diabetes in critically ill patients, improving outcomes and providing better results.

SUPPLEMENTARY INFORMATION

Funding: *No fund was received related to this study.*
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Informed Consent Statement: *Not applicable*
Data Availability Statement: *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
Conflicts of Interest: *The authors declare no conflicts of interest.*
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