

Incidence and outcomes of early hyperglycaemia in critically ill patients

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Background. Hyperglycaemia is common in hospitalised patients. Acute illness or injury may result in glucose intolerance and insulin resistance leading to hyperglycaemia. There is a lack of data on the incidence and impact of early hyperglycaemia in critically ill patients in South Africa (SA).

Objectives. To determine the incidence of hyperglycaemia within 48 hours of admission to a multidisciplinary SA ICU and to determine if there was any association between blood glucose level and ICU outcomes.

Methods. This was a retrospective observational study of patients admitted to ICU at King Edward VIII Hospital from November 2021 to August 2022. All blood glucose values were recorded within the first 48 hours of admission. The primary outcome was ICU mortality, with secondary outcomes including ICU length of stay (LOS), ventilator days (LOV), renal replacement therapy (RRT) and wound infection.

Results. A total of 177 patients were included in the study. Hyperglycaemia with a blood glucose of more than 10 mmol/L within 48 hours of ICU admission occurred more frequently in those who died in ICU (79.5%) v. ICU survivors (60.1%) ($p=0.026$). Hyperglycaemia was associated with an increase in ICU LOS, LOV and wound infection. No statistically significant relationship was found between hyperglycaemia and RRT. Hypoglycaemia within 48 hours of ICU admission was also associated with an increased ICU mortality.

Conclusion. Extremes of blood glucose were associated with increased ICU mortality. We recommend a moderate glycaemic control target of 6 - 10 mmol/L in resource-limited settings.

Keywords. hyperglycaemia; intensive care unit; glycaemic control; critical care; sepsis; shock; diabetes mellitus.

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Contribution of study

The study provides insight into associations with blood glucose level in a multidisciplinary critical care population in South Africa. Hyperglycaemia is common in critically ill patients in South Africa and is associated with severity of illness. Hyperglycaemia is associated with increased ICU mortality, ICU length of stay, length of ventilation and wound sepsis. Hypoglycaemia was also associated with increased ICU mortality. Based on the findings of this study, moderate glycaemic control, with avoidance of hypoglycaemia remains a reasonable strategy for critically ill patients in South Africa.

Hyperglycaemia is common in critically ill patients and is associated with increased morbidity and mortality.^[1,2] During acute illness, hyperglycaemia occurs due to several factors: including sepsis, counterregulatory hormones, drugs and parenteral nutrition.

Early trials showed that tight glycaemic control (4.4 - 6.1 mmol/L) improved outcomes of ICU patients, with a mortality reduction in surgical patients and a reduction in morbidity in medical ICU patients.^[3,4] Subsequent studies, however, did not replicate these findings and showed that tight glycaemic control was associated with increased adverse events.^[5,6] In the seminal NICE-SUGAR trial, intensive glucose control (target blood glucose 4.5 - 6.0 mmol/L) was associated with an increased risk of severe hypoglycaemia and increased mortality compared with 'conventional' glucose control (target blood glucose ≤ 10 mmol/L).^[5] Following these findings the current standard of care in critically ill patients is generally 'moderate' glycaemic control, with a target blood glucose of 6 - 10 mmol/L.^[5] The disparate findings do, however, suggest that the optimal glycaemic

target may be context specific, balancing the risks of hypoglycaemia with the benefits of glycaemic control.

Factors other than the specific glycaemic target also appear to be related to ICU outcome, with some studies reporting improved outcomes with a greater proportion of time spent in the target glycaemic range.^[7,8] Even with an established glycaemic target, achievement of this target varies and is an area of clinical care that is particularly amenable to quality improvement initiatives.^[9]

There is limited data on glycaemic control in the South African (SA) critical care setting. The only local study identified, evaluated adherence to a glucose control protocol by the nurses in a cardiothoracic intensive care unit.^[10] This study concluded that the blood glucose was out of range in 84.9% of readings and protocol violations occurred in 55.5% of readings. This was attributed to a shortage of qualified nursing staff. Based on this data, the feasibility and safety of utilising protocols from high-income countries in the resource-limited setting may be a concern. Further research is thus required to better describe loco-

regional glycaemic control data, describing the scope of the problem and identifying any particular areas of concern or potential intervention.

Critically ill populations and critical care practices vary, and it cannot be assumed that findings in one setting apply to a different setting. In a previous study from the study ICU, it was demonstrated that, while hyperlactataemia does identify a subset of vasopressor-requiring patients who have a high mortality (as per the Sepsis-3 definition), the optimal cut-off was higher in the SA cohort as opposed to the Sepsis-3 cohort.^[11,12] SA critical care populations differ in a number of respects from high-income countries in which most of the research in the field has taken place: *inter alia*, they tend to be younger with a higher burden of trauma and infectious diseases, and potentially differences in the prevalence of chronic diseases such as diabetes mellitus.^[13] There are also potential region-specific differences in therapeutic practices such as choice of vasoactive agent (adrenaline v. noradrenaline), utilisation of corticosteroids in septic shock, choice and timing of maintenance fluid, and nutritional support, all of which may impact on glycaemic control and potentially the response to hyperglycaemia. It is thus important to evaluate the potential impact of hyperglycaemia in SA critically ill patients and attempt to effectively manage it to improve the outcomes of these patients. This will allow for a more evidence-based approach to determine the recommended glycaemic range in a resource limited setting. To note, the differences in outcomes between the Leuven studies^[3,4] and NICE-SUGAR^[5] highlighted the fact that data from one centre or population cannot necessarily be extrapolated to other centres and populations. It is also reasonable to hypothesise that there may be differences between SA and high-income ICU populations. There are documented differences in median age, potential differences in admission pathology, severity of illness and comorbidities (including differences in diagnosis and management of comorbidities). There are also potential differences in therapeutic strategies e.g. corticosteroid usage for septic shock is likely to show regional differences and the use of adrenaline as opposed to noradrenaline in shock states (especially septic shock) is likely to influence rates, and potentially the impact, of hyperglycaemia. As an example, in previous research from the present study ICU it was shown that optimal lactate thresholds differed from those shown in the Sepsis-3 derivation cohorts.^[11]

Given the above considerations we decided to evaluate the incidence and outcomes of early hyperglycaemia in a heterogenous critically ill population in SA. The primary outcome was ICU mortality, with secondary outcomes including ICU length of stay (LOS), ventilator days (LOV), renal replacement therapy (RRT) and wound infection.

Methods

This was a retrospective observational study of patients admitted to the ICU at Victoria Mxenge Hospital (formerly King Edward VIII Hospital) from November 2021 to August 2022. The study ICU is a multidisciplinary, closed, intensivist-run ICU in a tertiary academic hospital that serves KwaZulu-Natal Province in SA.

Ethics

Approval for the study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC ref no. /00002646/2021), King Edward VIII Hospital (ref. no. XX) and the Health Research Committee of the KwaZulu-Natal Department of Health (ref. no. XX).

All patients presenting to ICU were included in the study provided they did not meet any of the following exclusion criteria:

- age less than 18 years
- died or discharged within 48 hours of admission
- no blood glucose results recorded within first 48 hours of ICU.

Data collection proceeded backwards sequentially from the date of first data collection, using stored ICU charts. Data collected included: demographics; disease data; severity of illness; outcomes; all blood glucose values recorded within the first 48 hours of admission; and insulin therapy. The primary outcome was ICU mortality, with secondary outcomes including ICU length of stay (LOS), ventilator days (LOV), renal replacement therapy (RRT) and wound infection. The sequential organ failure assessment (SOFA) score was used to assess organ dysfunction and define sepsis in the critically ill patient. An increase in SOFA score of two or more in patients with suspected infection was used to define sepsis. Shock was defined pragmatically as the need for inotropic/vasopressor support.

Blood glucose analysis was performed using bedside glucometers and capillary blood glucose. The glucometer used was the VivaChek Ino (VivaChek Biotech Co. (Ltd), China). Within-run precision testing data reports a coefficient of variation (CV) of 6.4 - 6.9% for blood glucose values between 1.7 mmol/L and 2.8 mmol/L and a CV of 2.7 - 2.9% for values between 13.9 mmol/L and 22.2 mmol/L. Reported performance data for this device in clinical use, includes a correlation coefficient of 0.988 for laboratory glucose analysis, with 98% of results being within 10% of the laboratory result and 100% of results being within 15% of the laboratory result. Hyperglycaemia was defined as a blood glucose level of more than 10 mmol/L (based on data from NICE-SUGAR^[5]) at any point during the specified time period. Two levels of low blood glucose (<6mmol/l and <4 mmol/L) were also evaluated based on thresholds previously explored in critical care literature. Hypoglycaemia was, however, defined as a blood glucose of less than 4 mmol/L at any point during the specified period. Summary data were analysed as a time-weighted average (TWA) per period. The TWA for a specific period was calculated as the mean of the sum of the products of blood glucose multiplied by the number of hours till the next blood glucose measurement.

$$TWA = \frac{(BGR1 \times (BGT2 - BGT1) + BGR2 \times (BGT3 - BGT2) \dots + BGRn \times (BGTn+1 - BGTn))}{(BGTn+1 - BGT1)}$$

where BGR = blood glucose reading; BGT = blood glucose time; and subscripts refer to the specific position in the sequence of readings during the time period of interest. A TWA was not calculated for an ICU Day if fewer than 4 readings were performed, or more than 6 hours had lapsed between the last reading and the end of the ICU Day. Assuming a baseline ICU mortality of 30% (historical data for the study ICU) and with the aim of detecting a ~10% difference in mortality based on the presence or absence of hyperglycaemia, with an alpha error of 0.05 and a power of 80%, a minimum sample size of 162 patients was calculated. It was decided that a total of 185 patients were to be included to allow for missing data and any subsequent exclusions. Statistical analysis was performed using IBM SPSS Statistics (version 28.0; IBM Corp. USA). Categorical variables were described as percentages and compared using the Chi-square test, Fisher's exact test, or Fisher-Freeman-Halton exact test, where appropriate. Continuous data were described using mean and standard deviation (SD) when normally distributed and the median and interquartile range (IQR) when the distribution was non-Gaussian. These data were compared using the independent samples *t*-test (with use of Levene's test for equality of variances) or Mann-Whitney *U*-test, respectively. Missing data were omitted and not imputed. A *p*-value of <0.05 was considered statistically significant. Multivariable analyses

were performed using binary logistic regression, using a backward stepwise (likelihood ratio) method. Variables were initially included if they had a *p*-value <0.1 on univariate analysis. To optimise the event-to-variable ratio and reduce the impact of collinearity, where variables were deemed to have a high risk of collinearity/to be highly correlated, a clinical decision was taken on the most appropriate variable to include in the model. A variable to event ratio of 12.6 was obtained for the multivariable analysis of hyperglycaemia within 48 hours and 4.2 for the analysis of ICU outcome.

Results

A total of 177 patients were included in the study. A flow chart of included and excluded patients is shown in Fig. 1. Demographic data and cohort characteristics are shown in Table 1. The age range was 18 to 89 years. Overall, 39 patients died in ICU, with an ICU mortality for the entire cohort of 22.0%. The length of ICU stay varied between 2 and 45 days and the SOFA score ranged from 0 to 19. The associations between demographic data, cohort characteristics, secondary outcomes and ICU mortality are also shown in Table 1. Table 2 shows the frequencies of blood glucose monitoring. A mean (SD) of 7.88 (1.85) blood glucose measurements were performed on ICU day 1, with a range of 5 to 16 measurements, while the mean (SD) number of measurements on ICU day 2 was 6.13 (2.06), with a range of 0 to 16 as shown in Table 2. Patients

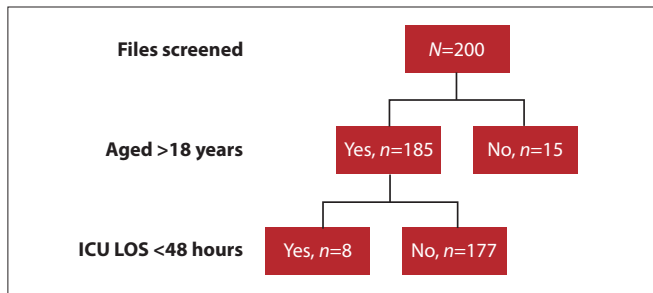


Fig. 1. Flowchart of included and excluded patients.

who died had significantly more blood glucose measurements on ICU-day 1 than those who survived, 8.49 (2.13) v. 7.70 (1.74) (*p*=0.019). There was no statistically significant difference in the number of blood glucose readings between non-survivors and survivors on ICU-day 2, 6.23 (2.84) v. 6.10 (1.80) (*p*=0.789). A total of 114 (64.4%; 95% CI 57.3 - 71.5) patients had at least one blood glucose reading >10 mmol/L during the first 48 hours of ICU admission, with 107 (60.5%; 95% CI 53.2 - 67.7) being hyperglycaemic on day 1 and 55 (31.4%; 95% CI 24.5 - 38.4) being hyperglycaemic on day 2. It was noted that 42 (23.7%) patients were hyperglycaemic on ICU admission. When the 27 patients who were known to be diabetic were excluded, 90 (60.0%) patients were hyperglycaemic within the first 48 hours of ICU admission. In contrast, the incidence of hyperglycaemia was 89% in patients who were known to be diabetic.

A flow chart detailing the glycaemic status of patients during the first 48 hours of ICU admission is shown in Fig. 2. The minimum and maximum blood glucose measurements on day 1 were 1.3 mmol/L and 32 mmol/L, respectively. The corresponding values for day 2 were 1.3 mmol/L and 21 mmol/L, respectively. The lowest TWA blood glucose on day 1 was 4.7 mmol/L, with the highest TWA being 19.5 mmol/L. The corresponding values for day 2 were 4.8 mmol/L and 14.3 mmol/L, respectively.

Table 3 evaluates potential predictors of hyperglycaemia during the first 48 hours of ICU admission. On multivariable analysis known diabetes (OR 6.32 (95% CI 1.66 - 24.02)) (*p*=0.007), shock on referral (OR 4.98 (95% CI 2.13-11.64)) (*p*<0.001) and an elevated lactate (OR 1.28 (95% CI 1.06 - 1.56) (*p*=0.011) remained significant predictors of hyperglycaemia within the first 48 hours of ICU admission.

Table 4 presents data on the potential associations between glycaemic data and ICU mortality. A sensitivity analysis was performed, excluding patients known to be diabetic, however, this did not change the association between hyperglycaemia within 48 hours and increased ICU mortality, (*p*=0.012). On multivariable analysis age (OR 1.05 (95% CI 1.02 - 1.08)) (*p*<0.001), any blood glucose <4 mmol/L in the first

Table 1. Demographics, cohort characteristics and ICU mortality

	Total (n=177) n (%)*	Survived (n=138), n (%)*	Died (n=39), n (%)*	<i>p</i> -value	
Age (years), mean (SD)	40 (17.0)	38 (15.0)	51 (19.0)	<0.001	
Sex	Female	74 (41.8)	57 (41.3)	17 (43.6)	0.798
	Male	103 (58.2)	81 (58.7)	22 (56.4)	
Referring discipline	Medicine	45 (25.4)	29 (21.0)	16 (41.0)	0.011
	O&G	22 (12.4)	21 (15.2)	1 (2.6)	
	Surgery	110 (62.1)	88 (63.8)	22 (56.4)	
Primary pathology	NCD	47 (26.6)	41 (29.7)	6 (15.4)	0.006
	Sepsis	74 (41.8)	49 (35.5)	25 (64.1)	
	Trauma	56 (31.6)	48 (34.8)	8 (20.5)	
Known diabetic	27 (15.3)	18 (13.0)	9 (23.1)	0.124	
Sepsis [†]	144 (81.4)	107 (77.5)	37 (94.9)	0.014	
Post surgery	99 (55.9)	82 (59.4)	17 (43.6)	0.079	
Shock on referral	95 (53.7)	63 (45.7)	32 (82.1)	<0.001	
Initial SOFA, mean (SD)	6.0 (3.2)	5.4 (3.0)	8.0 (2.8)	<0.001	
RRT	31 (17.5)	15 (10.9)	16 (41.0)	<0.001	
LOS (days), mean (SD)	5.4 (4.4)	4.9 (2.8)	7.2 (7.6)	0.072	
Ventilator days, mean (SD)	3.6 (4.3)	2.7 (1.9)	6.5 (7.6)	0.003	
Wound infection	13 (7.3)	7 (5.1)	6 (15.4)	0.040	

ICU = intensive care unit; SD = standard deviation; O&G = Obstetrics and Gynaecology; NCD = non-communicable disease; SOFA = Sequential Organ Failure Assessment (score); RRT = renal replacement therapy; LOS = length of stay.
 *Unless otherwise specified.
 †As primary or secondary diagnosis.

48 hours of ICU admission (OR 2.74 (95% CI 1.05 - 7.18) ($p=0.040$), post-surgical status (OR 0.17 (95% CI 0.06 - 0.52)) ($p=0.002$), and shock on referral (OR 4.35 (95% CI 1.20 - 15.75)) ($p=0.025$) remained significantly associated with ICU mortality.

Table 5 presents data on hyperglycaemia on day 1 and day 2 and the prespecified secondary outcomes. Insulin utilisation is shown in Table 6.

Discussion

This study provides the first data on the incidence and outcomes of early hyperglycaemia in critically ill patients from a SA multidisciplinary ICU. Our cohort differs from those in other studies conducted in high-income countries in terms of demographics.^[3,4,5] The mean age of our cohort was only 40 years, in keeping with data from lower income countries.^[13] In

comparison, in the NICE-SUGAR^[5] trial and both the first and second Leuven trials,^[3,4] the mean age was 60 years or older.^[3,4,5] Our cohort involved a population with a high incidence of sepsis and trauma. It was also a relatively heterogenous cohort: just over half were postoperative (56%), almost one-third (32%) had suffered trauma and a quarter (25%) were medical patients. No cardiothoracic patients were present in the study cohort. We had a high burden of sepsis (81% as either a primary or secondary diagnosis). With respect to severity of illness, despite the young median age, the cohort had a relatively high mean SOFA score of 6, an ICU mortality of 22% and over half (54%) of patients had shock on referral. In contrast, in the NICE-SUGAR trial,^[5] only 37% were postoperative, 15% had suffered trauma and 22% had severe sepsis on randomisation. ICU mortality was slightly lower at 17%. The first

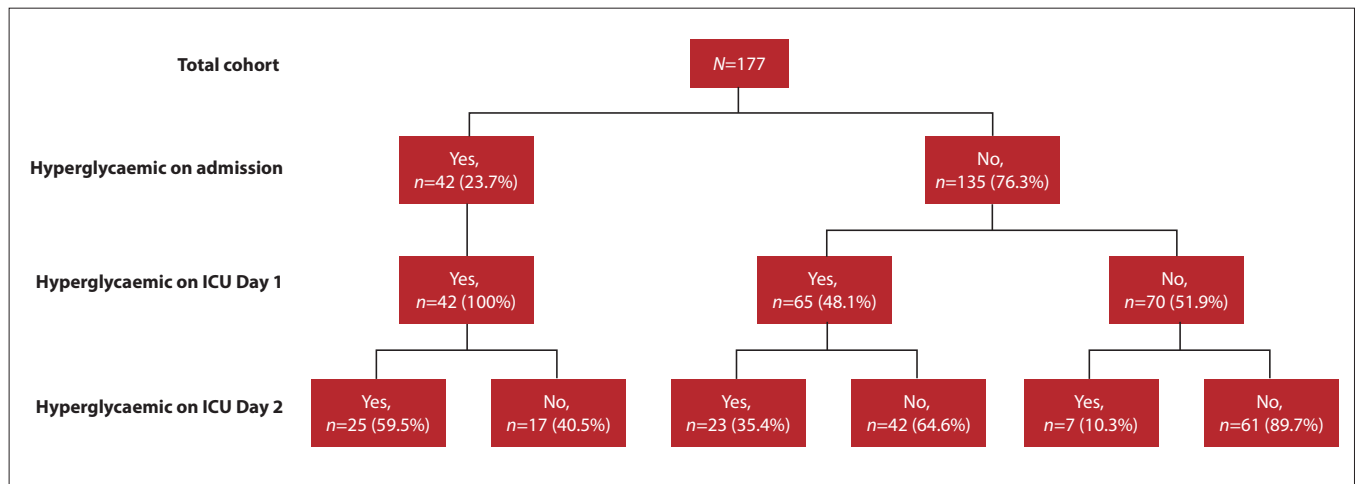


Fig. 2. Flowchart detailing the glycaemic status of patients during the first 48 hours of ICU admission.

Table 2. Frequencies of blood glucose monitoring in the ICU

Blood glucose measurements, n	Entire cohort		Survived		Died		p-value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
First 24 hours	7.88 (1.85)	5 - 16	7.70 (1.74)	5 - 14	8.49 (2.13)	6 - 16	0.019
24 - 48 hours	6.13 (2.06)	0 - 16	6.10 (1.80)	0 - 13	6.23 (2.84)	0 - 16	0.789

Table 3. Analysis of factors potentially associated with hyperglycaemia within the first 48 hours of ICU admission

	Entire cohort (n=177), n (%)*	No hyperglycaemia (n=63), n (%)*	Hyperglycaemia (n=114), n (%)*	p-value
Age (years), mean (SD)	40.0 (17.0)	36.0 (13.0)	43.0 (18.0)	0.002
Sex				
Female	74 (41.8)	25 (39.7)	49 (43.0)	0.670
Male	103 (58.2)	38 (60.3)	65 (57.0)	
Primary pathology				
NCD	47 (26.6)	25 (39.7)	22 (19.3)	<0.001
Sepsis	74 (41.8)	14 (22.2)	60 (52.6)	
Trauma	56 (31.6)	24 (38.1)	32 (28.1)	
Post surgery	99 (55.9)	31 (49.2)	68 (59.6)	0.180
Sepsis [†]	144 (81.4)	48 (76.2)	96 (84.2)	0.190
Known diabetic	27 (15.3)	3 (4.8)	24 (21.1)	0.004
Shock on referral	95 (53.7)	13 (20.6)	82 (71.9)	<0.001
Initial SOFA score, mean (SD)	6.0 (3.2)	4.8 (2.9)	6.6 (3.1)	<0.001
Lactate (mmol/L), mean (SD)	4.0 (3.1)	2.4 (1.5)	4.8 (3.5)	<0.001
Use of corticosteroids on day 1	75 (42.4)	12 (19.0)	63 (55.3)	<0.001
Use of inotropes on day 1	92 (52.0)	13 (20.6)	79 (69.3)	<0.001
Enteral nutrition	60 (33.9)	28 (44.4)	32 (28.1)	0.028
Parenteral nutrition	8 (4.5)	2 (3.2)	6 (5.3)	0.714

ICU = intensive care unit; SD = standard deviation; NCD = non-communicable disease; SOFA = Sequential Organ Failure Assessment (score).

*Unless otherwise specified.

[†]As primary or secondary diagnosis.

Table 4. ICU outcome and glycaemic data

	Entire cohort, n (%)*	Survived, n (%)*	Died, n (%)*	p-value
Hyperglycaemia day 1	107 (60.5)	80 (58.0)	27 (69.2)	0.204
Minimum BG day 1 (mmol/L), mean (SD)	5.63 (1.69)	5.66 (1.54)	5.55 (2.17)	0.771
Maximum BG day 1 (mmol/L), mean (SD)	12.53 (5.12)	12.03 (4.63)	14.29 (6.32)	0.015
Any BG <4 mmol/L day 1	29 (16.4)	20 (14.5)	9 (23.1)	0.201
Any BG <6 mmol/L day 1	109 (61.6)	87 (63.0)	22 (56.4)	0.452
All BG readings 6 - 10 mmol/L day 1	18 (10.2)	17 (12.3)	1 (2.6)	0.129
Proportion of values >10 mmol/L day 1, mean (SD)	0.26 (0.28)	0.25 (0.27)	0.33 (0.30)	0.123
TWA BG day 1 (mmol/L), mean (SD)	8.75 (2.36)	8.57 (2.27)	9.41 (2.60)	0.050
TWA BG >10 mmol/L day 1	43 (24.3)	29 (21.0)	14 (35.9)	0.056
Hyperglycaemia day 2	55 (31.4)	41 (29.9)	14 (36.8)	0.417
Minimum BG day 2 (mmol/L), mean (SD)	5.74 (1.65)	5.76 (1.35)	5.67 (2.46)	0.831
Maximum BG day 2 (mmol/L), mean (SD)	9.60 (3.06)	9.33 (2.93)	10.59 (3.37)	0.025
Any BG <4 mmol/L on day 2	21 (12.0)	10 (7.3)	11 (28.9)	<0.001
Any BG <6 mmol/L on day 2	108 (61.7)	87 (63.5)	21 (55.3)	0.355
All BG readings 6 - 10 mmol/L day 2	44 (25.1)	33 (24.1)	11 (28.9)	0.541
Proportion of values >10 mmol/L day 2, mean (SD)	0.13 (0.22)	0.12 (0.21)	0.17 (0.26)	0.224
TWA BG Day 2 (mmol/L), mean (SD)	7.58 (1.56)	7.51 (1.53)	7.85 (1.69)	0.300
TWA BG >10 mmol/L day 2	12 (8.1)	7 (5.9)	5 (17.2)	0.059
Hyperglycaemia within 48 hours	114 (64.4)	83 (60.1)	31 (79.5)	0.026
Any BG <4 mmol/L in first 48 hours	44 (24.9)	28 (20.3)	16 (41.0)	0.008
Any BG <6 mmol/L in first 48 hours	137 (77.4)	109 (79.0)	28 (71.8)	0.343
All BG readings 6 - 10 mmol/L in first 48 hours	10 (5.6)	9 (6.5)	1 (2.6)	0.694
TWA BG first 48 hours (mmol/L), mean (SD)	8.31 (1.99)	8.15 (1.88)	8.88 (2.29)	0.097
TWA BG >10 mmol/L in first 48 hours	16 (10.8)	12 (10.1)	4 (13.8)	0.519

ICU = intensive care unit; BG = blood glucose, SD = standard deviation; TWA = time-weighted average.
*Unless otherwise specified.

Table 5. Associations between selected glycaemic data and secondary outcomes

		LOS (days)		LOV (days)		RRT		Wound infection	
		Mean (SD)	p-value	Mean (SD)	p-value	n (%)	p-value	n (%)	p-value
Hyperglycaemia day 1	Yes (n=107)	6.0 (5.2)	0.027	4.2 (5.3)	0.068	23 (21.5)	0.085	9 (8.4)	0.501
	No (n=70)	4.5 (2.5)		2.7 (1.9)		8 (11.4)		4 (5.7)	
Hyperglycaemia day 2	Yes (n=55)	5.8 (4)	0.078	4.0 (3.2)	0.012	13 (23.6)	0.123	8 (14.5)	0.026
	No (n=120)	5.3 (4.6)		3.4 (4.7)		17 (14.2)		5 (4.2)	

LOS = ICU length of stay; LOV = length of ventilation; RRT = renal replacement therapy.

Table 6. Insulin utilisation in ICU

	Total, n (%)*	Survived, n (%)*	Died, n (%)*	p-value
Insulin use on day 1	85 (48.0)	63 (45.7)	22 (56.4)	0.235
Insulin use on day 2	59 (33.3)	45 (32.6)	14 (35.9)	0.700
Insulin use in first 48 hours	91 (51.4)	68 (49.3)	23 (59.0)	0.285
Insulin dose day 1 (units), mean (SD)	52.95 (55.28)	49.62 (52.64)	62.5 (62.54)	0.350
Insulin dose day 2 (units), mean (SD)	22.17 (22.84)	22.78 (23.88)	20.21 (19.79)	0.717
Insulin dose first 48 hours (units), mean (SD)	63.84 (64.83)	61.04 (63.53)	72.09 (69.32)	0.483

ICU = intensive care unit; SD = standard deviation.
*Unless otherwise specified.

Leuven study included surgical patients only, with almost two thirds (63%) being cardiac surgery patients, and as expected ICU mortality was only 6% - this study population bears little resemblance to our patient population.^[3] In the second Leuven study, only medical ICU patients were included with a mortality of 26% which was similar to the study cohort. However, in most other respects it is difficult to compare an elderly medical ICU population with our younger, heterogenous population.^[4] Our study thus provides real-world data on glycaemic

control in critical care in resource-limited countries as opposed to the landmark studies from high-income countries.^[3,4,5]

The incidence of hyperglycaemia was 23.7% on admission in our study. This was high compared with the first Leuven study where the incidence was only 12% and the Laird study, where it was 17.4%.^[2,3] However, it was similar to a study by Van Vught *et al.*,^[14] where the incidence was 20.2% in a mixed medical and surgical ICU cohort, similar to our cohort. Christiansen *et al.*,^[15] however, reported a much

higher incidence of 54.1%, with similar cohort characteristics. We noted discrepancies in the timing and definition of hyperglycaemia in these studies and thus it is difficult to compare the incidence of hyperglycaemia between studies. Only 15.3% of patients in our study were known to be diabetic, yet 64.4% of the study population had hyperglycaemia within 48 hours of admission. Our study mirrors the relatively low incidence of diabetic patients in the NICE-SUGAR trial,^[5] with 20.4% in the intensive group and 19.8% in the conventional group, and in the first Leuven trial (13%).^[3] The high incidence of hyperglycaemia could reflect patients with undiagnosed diabetes but most likely highlights the frequency, importance, and the complications of stress hyperglycaemia in critical illness. ICU therapies may also have an impact on the incidence and outcomes of hyperglycaemia. Comparisons between studies are difficult because of inconsistent reporting in this regard. Corticosteroids are one such therapy. Corticosteroids were administered on ICU-day 1 in 42% of patients in our cohort and the incidence of hyperglycaemia was significantly higher in those that received corticosteroids. This may be due to the corticosteroid therapy but is more likely a reflection of the severity of illness, as corticosteroids would generally be prescribed as adjunctive therapy for septic shock. In NICE-SUGAR^[5] only 33% of patients received corticosteroids, while 54% received them in the Leuven 2 trial.^[4] Caloric load may also impact on glycaemic control. Hyperglycaemia was less common in patients receiving early enteral nutrition. This may reflect differences in disease severity, with enteral nutrition likely to be delayed in patients with unstable shock states. Patients who do not receive enteral nutrition would generally receive a 10% dextrose-containing intravenous maintenance fluid, and the increased risk of hyperglycaemia may also be due to this intervention. The use of adrenergic agonists, especially adrenaline may reasonably be expected to predispose to hyperglycaemia. This was noted in our study, with patients receiving inotropes (adrenaline being the agent of choice in the study ICU) being significantly more likely to be hyperglycaemic. It is however difficult to differentiate whether this association reflects an effect of the adrenergic agonist itself or rather the shock state that necessitated the use of an adrenergic agonist. It is worth noting, however, that in the Van Vught *et al.* study,^[14] the incidence of shock was higher in euglycaemic patients.

Diabetic patients were more likely to be hyperglycaemic during the first 48 hours of ICU admission. This was an expected finding and reflects the reduced ability to adapt to stress-induced hyperglycaemia. We also found that patients with hyperglycaemia were older than those without hyperglycaemia (although the median age was relatively young in both groups). This could reflect an increased prevalence of diabetes (both diagnosed and undiagnosed) with increasing age. Aging also results in impaired pancreatic B cell function leading to insulin deficiency and resistance.^[16] Older patients may thus be more likely to be hyperglycaemic during critical illness, due to differences in the incidence of diabetes, the stress response, the primary pathology or severity of illness. Other predictors of hyperglycaemia on univariate analysis included the primary pathology (with an increased risk in sepsis), shock, the use of corticosteroids, a high total SOFA score and a high lactate. Only the presence of diabetes, shock and an elevated lactate remained predictors of outcome on multivariable analysis, however, suggesting that the severity of the critical illness and an underlying impairment in the physiological response to stress-induced hyperglycaemia are the important determinants of the hyperglycaemic response in critical illness.

Our study showed that hyperglycaemia, with a blood glucose of more than 10 mmol/L within 48 hours of ICU admission, was more common

in those who died in ICU (79.5%) compared with ICU survivors (60.1% ($p=0.026$)). This was in keeping with the conclusion of the NICE-SUGAR trial,^[5] which recommends maintaining the blood glucose level below 10 mmol/L, as it is associated with lower mortality. We also showed that the maximum blood glucose on day 1 and day 2 was significantly higher in patients who died in ICU, this being most marked on day 1 where the mean highest blood glucose was 14.3 mmol/L in those who died, as opposed to 12.0 mmol/L in those who survived. We hypothesised that both the severity and duration of hyperglycaemia would be significantly associated with increased ICU mortality and thus included analysis of the TWA blood glucose. Contrary to expectations, the TWA blood glucose was not statistically significantly higher in non-survivors (although it was numerically higher). Similarly, the proportion of blood glucose values >10 mmol/L did not differ significantly between survivors and non-survivors. Taken together this data may suggest that high peaks of blood glucose may be more injurious than lower sustained elevations in blood glucose, although avoiding a blood glucose >10 mmol/L remains a reasonable target. This finding may also reflect the importance of glycaemic variability in critical illness which has been postulated to be a marker of disease severity.^[17] Further studies are, however, needed to evaluate and confirm the effects of glycaemic variability in critically ill patients. To avoid glycaemic variability, protocols should be implemented in the ICU to avoid extremes of blood glucose and to maintain euglycaemia.

While there was no difference in minimum blood glucose values between those who survived in ICU and those who did not, we noted that patients who died were significantly more likely to have had at least one blood glucose of <4 mmol/L in the first 48 hours of ICU admission. There was an increased mortality associated with a blood glucose of <4 mmol/L on day 2 (52.4% v. 17.5% ($p=0.001$)). This difference was not statistically significant on day 1 although there was still a numerically increased mortality in those with a blood glucose of <4 mmol/L on day 1 (35.5% v. 22.1% ($p=0.112$)). Similarly, on multivariable analysis, the only glycaemic control variable that remained significantly associated with increased ICU mortality, was a blood glucose <4 mmol/L during the first 48 hours of ICU admission. Our data support avoiding significant hypoglycaemia with a blood glucose <4 mmol/L. While this may simply be correlation, and not necessarily causation, this aligns with other published literature, particularly the NICE-SUGAR trial.^[5,6] The known detrimental effects of hypoglycaemia are multifactorial. It has been postulated that while hypoglycaemia normally triggers the release of glucagon, cortisol, adrenaline and growth hormone to restore normoglycaemia, in critically ill patients this physiological response is blunted.^[18] Hypoglycaemia has also been associated with increased risk of cardiac arrhythmias in diabetic patients.^[19] Of note, there was no significant association between a blood glucose of <6 mmol/L and ICU mortality at any time period, although at all time points, ICU mortality was numerically lower in those with a blood glucose of <6 mmol/L. This may be taken as evidence to support the tight glycaemic control targets used in the first and second Leuven studies.^[3,4] However, the NICE-SUGAR trial^[5] and VISEP^[6] both caution against this approach as hypoglycaemia occurs more commonly while trying to achieve tight glycaemic control in critically ill patients and was associated with an increase in mortality.

We also found that hyperglycaemia was associated with an increase in ICU LOS and LOV compared to patients with normoglycaemia. While the statistical significance of these findings is inconsistent, the large absolute difference of 1.5 days for LOS and LOV for hyperglycaemia

on ICU day 1 suggests that this finding is clinically relevant. One of the reasons that could explain this finding is that hyperglycaemia causes myopathy that impairs weaning from mechanical ventilation and therefore prolonging ICU stay.^[16] Therefore, intensive insulin therapy to promote normoglycaemia may reduce this complication.^[20] The relatively short ICU LOS makes this explanation less likely though and this association may simply reflect differences in illness severity. No statistically significant relationship between hyperglycaemia and RRT was noted during the study, however this may be due to a type II statistical error due to the low number of patients receiving RRT in this study. Hyperglycaemia is known to produce a higher rate of infections.^[2] Our study showed that patients with hyperglycaemia had higher incidence of wound infection even though the data was statistically significant only on ICU day 2 ($p=0.022$).

While not an interventional study, the data from this trial does provide some guidance for glycaemic control in the resource-limited setting. Extremes of blood glucose are to be avoided. Hypoglycaemia and hyperglycaemia are both associated with increased mortality and should be avoided. Our data suggests that a blood glucose target of 4 - 10 mmol/L is reasonable, however, given the risk of hypoglycaemia with tight glycaemic control (4.5 - 6.0 mmol/L) shown in the NICE-SUGAR trial,^[5] and adverse outcomes shown in this study with blood glucose values <4mmol/L, we suggest that the current generally accepted standard of moderate glycaemic control in the 6 - 10 mmol/L range remains most appropriate in resource-limited settings.

Study limitations

This study was a retrospective study using routinely collected data from the ICU at Victoria Mxenge Hospital. While the ICU does have a glycaemic control protocol, the present study did not evaluate adherence to the protocol. Blood glucose was predominantly measured with bedside glucometers for the measurement of capillary blood glucose, which might be a potential limitation in critically ill patients. The study was powered for a moderate difference in mortality of 10%, while in keeping with effect sizes previously reported in the literature, this is higher than the effect size in the NICE-SUGAR trial (2.6%) and thus false negative results cannot be excluded. Given the relatively small sample size, low variable to event ratio and variable selection strategy the multivariable logistic regression analyses may be at increased risk of bias/imprecision. While the ICU is a busy provincial referral centre, results are not necessarily generalisable to all centres. This is however the first such data that we are aware of in SA and given the broad concordance with international data we believe that it has reasonable external validity.

Conclusion

Hyperglycaemia was common in this heterogenous cohort of critically ill SA patients. Diabetes, shock on referral and elevated lactate were predictors of hyperglycaemia on multivariable analysis. Both early hyper- and hypoglycaemia were associated with increased ICU mortality, however, only early hypoglycaemia was a predictor of ICU mortality on multivariable analysis. We recommend a moderate glycaemic control target of 6 - 10 mmol/L in resource-limited settings.

Data availability. The data used for this study are available from the authors on request.

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