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Independent Association of Glucose Variability With Hospital Mortality in Adult Intensive Care Patients: Results From the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Binational Registry

Hemant Kulkarni, MD[1]; Shailesh Bihari, MD, FCICM, PhD[2]; Shivesh Prakash, MD, MPH, EDIC, FCICM[2]; Sue Huckson, BAppSci (Health Promotion)[3]; Shaila Chavan, MSPH[3]; Manju Mamtani, MD[1]; David Pilcher, MRCP, FRACP, FCICM[3–5]

[1]M&H Research, LLC, San Antonio, TX.

[2]Department of Critical Care Medicine, College of Medicine & Public Health, Flinders University and Flinders Medical Centre, Adelaide, SA, Australia.

[3]The Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE), Camberwell, VIC, Australia.

[4]The Department of Intensive Care, Alfred Health, Commercial Road, Prahran, VIC, Australia.

[5]The Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Commercial Road, Prahran VIC, Australia.

Drs. Kulkarni and Mamtani researched data and wrote the article. Drs. Kulkarni, Bihari, and Mamtani conceptualized the research. Drs. Huckson, Chavan, and Pilcher provided the data. Drs. Kulkarni and Mamtani take full responsibility for data integrity and analyses. All authors reviewed/edited the article.

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The data that support the findings of this study are available from Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of ANZICS CORE.

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For information regarding this article, E-mail: hemant.kulkarni@mnhresearch.com

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Objectives: Wide variations in blood glucose excursions in critically ill patients may influence adverse outcomes such as hospital mortality. However, whether blood glucose variability is independently associated with mortality or merely captures the excess risk attributable to hyperglycemic and hypoglycemic episodes is not established. We investigated whether blood glucose variability independently predicted hospital mortality in nonhyperglycemic critical care patients.

Design: Retrospective, registry data analyses of outcomes.

Setting: Large, binational registry (Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database repository) of 176 ICUs across Australia and New Zealand.

Patients: We used 10-year data on nonhyperglycemic patients registered in the Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database repository ($n = 290{,}966$).

Interventions: None.

Measurements and Main Results: Glucose variability was captured using glucose width defined as the difference between highest and lowest blood glucose concentration within first 24 hours of ICU admission. We used hierarchical, mixed effects logistic regression models that accounted for ICU variation and several fixed-effects covariates. Glucose width was specifically and independently associated with hospital mortality. The association of blood glucose variability with mortality remained significant (odds ratio for highest vs lowest quartile of glucose, 1.43; 95% CI, 1.32–1.55; $p < 0.001$) even after adjusting for the baseline risk of mortality, midpoint blood glucose level, occurrence of hypoglycemia and inter-ICU variation.

Mixed effects modeling showed that there was a statistically significant variation in this association across ICUs.

Conclusions: Our study demonstrates that glucose variability is independently associated with hospital mortality in critically ill adult patients. Inclusion of correction for glucose variability in glycemic control protocols needs to be investigated in future studies.

Key Words: critically ill; glucose variability; hospital mortality; hypoglycemia

The putative contribution of glucose variability with adverse outcome in critically ill patients is far from established. Demonstrating this association is challenging for several reasons. First, association of higher glucose variability with mortality may be confounded by hyperglycemia (1) or hypoglycemia (2, 3). Second, the measurement of glucose variability is neither straightforward nor consistent across studies. Rodbard (4, 5) has elegantly reviewed important current roadblocks to measurement of glycemic variation including the novelty (and therefore the immaturity) of the field. Third, the mechanistic basis of why glucose variability would influence hospital mortality is unclear despite observed correlation with oxidative stress (6). Fourth, in addition to the factors mentioned above the observational studies that form the basis of the putative association tend to be influenced by reporting bias as demonstrated by Eslami et al (7) in a review of 12 cohort studies published around the world in nondiabetic ICU patients with stress hyperglycemia. Considering these challenges and powered by the large, binational repository of ICU patients in Australia and New Zealand, we tested the hypothesis that glucose variability is independently associated with hospital mortality in nonhyperglycemic ICU patients.

MATERIALS AND METHODS

We used the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD, https://www.anzics.com.au/wp-content/uploads/2018/08/ANZICS-CORE-APD-Activity-Report-2016-17.pdf), one of the largest such datasets in the world with over 2 million ICU admissions (https://www.anzics.com.au/adult-patient-database-apd/). The registry has information on the sociodemographic variables, severity, comorbidity, biochemistry, and outcomes on all ICU admissions in 181 ICUs across Australia and New Zealand. This study was approved by the Institutional Review Board, University of Texas Rio Grande Valley, Brownsville, Texas, and by the ANZICS Centre for Outcome and Resource Evaluation (CORE) Management Committee.

Inclusion Criteria

Reporting diabetes (especially type 1 diabetes) was made mandatory by the ANZICS CORE Committee in 2007. Therefore, we constrained our dataset to years 2007–2016 (n = 983,555). From this, we included all the patients on whom the following data was available: lowest blood glucose level (BGL), highest BGL, hospital death, severity of illness (SOI) score baseline risk, and a glycemic status. As shown in the detailed inclusion protocol is shown in **Figure 1**, majority of the patients were excluded since at least one of their glucose measurements was outside the nonhyperglycemic range. Euglycemia was defined as highest BGL less than 7.78 mmol/L and lowest BGL value greater than or equal to 3.33 mmol/L, respectively whereas hypoglycemia was defined as any BGL value less than 3.33 mmol/L.

Outcomes and Predictors

The outcome of interest in this study was hospital death. In the ANZICS CORE database, the BGL measurements in the first 24 hours of admission are reported as the highest value and lowest value—entire set of measured BGL values are not available. Therefore, glucose variability was captured using glucose width which was defined as the difference between the highest and lowest BGL values. Average BGL was captured as the midpoint of the range from lowest to highest BGL values and referred to here as midpoint BGL (MBGL). The appropriateness of these two measures in the context of glucose variability was determined in a publicly available dataset of continuous glucose monitoring in 70 diabetic patients (https://archive.ics.uci.edu/ml/datasets/diabetes). Details of the dataset, the methods and results of these proof-of-concept studies are provided in **Supplementary Note 1** and **Supplementary Figure 1** (Supplemental Digital Content 1, http://links.lww.com/CCX/A73). SOI was estimated using Australia and New Zealand Risk of Death (ANZROD) (8), an adaptation of the Acute Physiology and Chronic Health Evaluation (APACHE) III scoring system, derived and calibrated for the Australian and New Zealand population. This model accounts for age, chronic health status, acute physiology, admission diagnosis, and additional locally available variables such as the presence of treatment limitations at admission to the ICU. To avoid confounding from glucose information already included within the overall predicted mortality risk, BGL values were regressed out of the ANZROD model. This corrected ANZROD mortality prediction (referred to as the SOI score) was then used in analyses.

Statistical Analysis

Because the dataset is contributed to by many ICUs with differing case mix and local population characteristics, all association analyses were conducted under the framework of hierarchical, mixed effects models. Specifically, we ran a series of mixed-effects logistic regression analyses wherein the ICU identifier was used as a random-effects variable. Thus, all the results are adjusted for potential inter-ICU variation. Additionally, these models permitted us to estimate the median odds ratio (MOR) and its 95% credible interval to quantify and statistically test the existence of inter-ICU variation (9). Robustness of associations was examined using sensitivity analyses for unmeasured and measured confounding. All statistical analyses were conducted using the Stata 12.0 (Stata Corp, College Station, TX) software package. Statistical significance was tested at a type I error rate of 0.05.

RESULTS

We included 290,966 nonhyperglycemic patients from 176 ICUs of whom 8% died during index hospitalization. Clinical characteristics of these patients are detailed in **Table 1**. Briefly, majority of the patients were 60 years old or more years, were female, generally

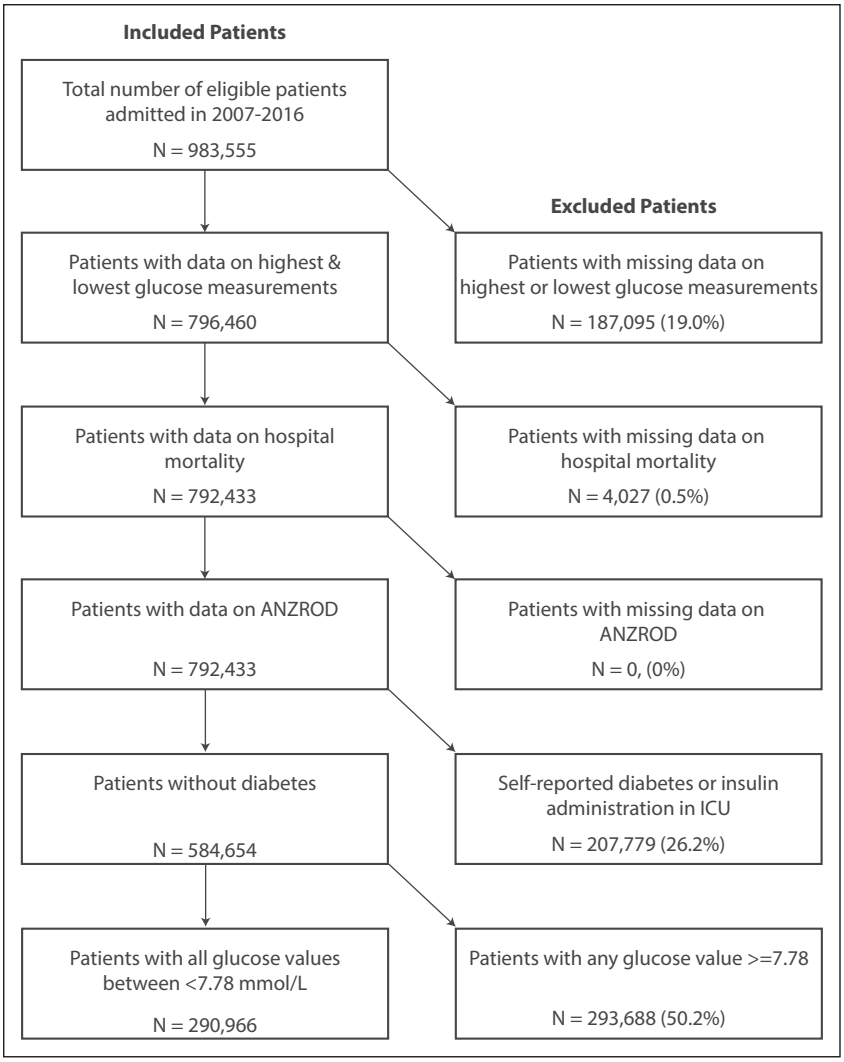

Figure 1. Inclusion protocol. The figure shows the inclusion protocol for the final sample size of 290,066 patients. The percentages shown in the *boxes* on the right-hand side use the previous *box* on the left as the denominator. For example, for missing data on death, the percentage (0.5%) is calculated as patients with missing death data ($n = 4,027$) from the 796,460 patients on whom glucose measurements were available. ANZROD = Australia and New Zealand Risk of Death.

nonobese, normotensive and included ~8% of the indigenous population with a prevalence of hypoglycemia at 2.6%. The Glasgow Coma Scale (GCS) indicated a mild affliction if any with average GCS score of 13.46 and the patients had a relatively healthy blood profile as indicated by hemoglobin concentration and blood cell counts. In general, patients who died as compared those who survived were older, less likely to have been admitted for elective surgery, more likely to have been admitted for intensive rather than high dependency care, lower GCS scores and higher white cell count (Table 1). Notably, the patients who died had very high SOI at admission as well as strikingly high APACHE III scores (Table 1).

The average glucose width was 0.51 mmol/L (SD 0.46 mmol/L) which was higher in those who died (0.68 mmol/L) as compared with those who survived (0.49 mmol/L; **Supplementary Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCX/A73). We, next, ran four hierarchical mixed effects models. Within each model, we compared the association of each quartile of glucose width with hospital death using the lowest quartile of glucose width as the reference category. The first model (column labeled Unadjusted in **Table 2**) shows unadjusted results. There was a stepwise increase in the odds ratio (OR) for each quartile of the glucose width from 1.13 for the second, to 1.35 for the third to 1.96 for the fourth quartile, all of which were strongly significant.

Next, even though hypoglycemia was a significant predictor of death (OR, 4.44; 95% CI, 4.27–4.62; $p < 1.0 \times 10^{-317}$), the association of glucose width with hospital death remained significant after adjustment for hypoglycemia. Even after addition of the corrected SOI score as a covariate, the association between glucose width and hospital death remained significant—the ORs for the second, third, and fourth quartiles were 1.07, 1.19, and 1.43, respectively.

As shown in **Supplementary Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCX/A73), the MBGL levels varied significantly and concordantly with the quartiles of glucose width. Thus, we also corrected the association for MBGL values. We observed (last column, Table 2) that after accounting for the MBGL levels, the association of glucose width quartiles with hospital death was stronger and was similar in strength. Notably, the final model showed a significant variation in the association across ICUs. The MOR was 1.46 (95% credible interval, 1.39–1.55) indicating that the high propensity ICUs are 46% more likely to find an association than a low propensity ICU for a clinically identical patient profile.

Finally, we determined the specificity and independence of the observed association between glucose width quartiles and hospital mortality. For this, we conducted additional mixed effects modeling analyses wherein widths (difference between highest and lowest value within first 24 hr) for the following six variables were added to the last model in Table 2: hemoglobin concentration, hematocrit, systolic blood pressure, diastolic blood pressure, white cell count, and platelet count. In these analyses, we tested the hypothesis that the quartiles of glucose width continue to remain statistically significantly associated with hospital mortality with these additional covariates. As shown in **Supplementary Table 2** (Supplemental Digital Content 1, http://links.lww.com/CCX/A73), our analyses indicated that the glucose width quartiles were consistently and significantly associated with hospital mortality even in the face of these covariates. Furthermore, with the exception of diastolic blood pressure variability, all other covariates were not significantly associated with hospital mortality indicating that the observed association between glucose width and hospital mortality was both independent and specific.

DISCUSSION

This is the largest study of nonhyperglycemic ICU patients that clearly demonstrates the independent and specific association of glucose variability with hospital. By design, the study eliminated a

TABLE 1. Characteristics of the Patients Included in the Study

Characteristic	Patients Alive at Discharge, *n* = 267,624	Patients Who Died in Hospital, *n* = 23,342
Age, yr, mean (SE)	57.0 (0.04)	68.9 (0.10)
Age ≥ 60 yr, *n* (%)	133,873 (50.0)	17,471 (74.9)
Females, *n* (%)	150,083 (56.0)	13,597 (58.3)
Indigenous, *n* (%)	17,497 (8.1)	1,365 (7.2)
Body mass index, mean (SE), kg/m^2	29.0 (0.18)	27.3 (0.30)
Elective surgery, *n* (%)	104,229 (39.1)	2,831 (12.2)
Type of care for which admitted, *n* (%)[a]		
Intensive care	196,232 (74.0)	19,398 (83.9)
High dependency	68,932 (26.0)	3,730 (16.1)
Average BP, mm Hg, mean (SE)		
Systolic BP	123.7 (0.07)	105.9 (0.27)
Diastolic BP	64.0 (0.04)	54.7 (0.13)
Glasgow Coma Scale score, mean (SE)		
Eye	3.60 (0.002)	3.10 (0.008)
Motor	5.61 (0.002)	4.81 (0.013)
Verbal	4.42 (0.002)	3.60 (0.011)
Total	13.63 (0.006)	11.51 (0.031)
Blood counts, mean (SE)		
Hemoglobin, g/dL	11.4 (0.005)	10.5 (0.0161)
Hematocrit, %	33.9 (0.01)	31.7 (0.05)
White cell count, × 10^9/L	11.3 (0.01)	13.5 (0.09)
Platelet count, × 10^9/L	219.3 (0.22)	202.4 (0.96)
Severity of illness score, mean (SE), × 100		
Raw	5.16 (0.02)	35.57 (0.18)
Corrected for glucose	4.71 (0.02)	34.84 (0.18)
Acute Physiology and Chronic Health Evaluation III score, mean (SE)	47.18 (0.04)	87.72 (0.21)

BP = blood pressure.

possible confounding by hyperglycemia and by way of analysis it accounted for the potential confounding by hypoglycemia. Despite additionally adjusting for a complex baseline SOI score that relies on many patient characteristics (10), for the risk of hypoglycemia, for MBGL and for inter-ICU variation, the association remained significant. These results strengthen the view that glucose variability, even in euglycemia, may be a third, orthogonal dimension of hospital mortality in ICU patients. This finding supports the increasing interest in the last decade on the importance of glucose variability in critical care (11–14). Of note, there was a significant inter-ICU variability in the observed associations which can be conceptually be explained by variability in glucose measurement methods, case-mix, treatment protocols, and annual volume of patients.

Some limitations of this study need to be recognized. First, our study presents another candidate measure of glucose variability (glucose width) which is simple and reasonably well correlated with currently used measures (as shown in Supplementary Note 1, Supplemental Digital Content 1, http://links.lww.com/CCX/A73). However, the value of this simple measure in clinical settings will need to be robustly investigated. In the ANZICS CORE database, we were constrained by the nonavailability of all glucose measurements within the first 24 hours, and therefore it was not possible to directly compare the validity of this measure against other accepted measures (15) of glucose variability. However, our proof-of-principle studies indirectly support the use of glucose width as a simple and reasonably accurate measure of glucose variability. Second, we demonstrated a significant variation across ICUs of the glucose variability → hospital mortality nexus. The factors that can contribute to this variation are currently unknown and need to be evaluated in future studies. Third, the observational nature

TABLE 2. Independent Association of Glucose Concentration Variability With Hospital Mortality

Model Component	Unadjusted[a]	Adjusted for Hypoglycemia	Adjusted for Hypoglycemia and Corrected SOI	Adjusted for Hypoglycemia, Corrected SOI and Midpoint of Blood Glucose Level
Quartile of glucose width				
1st	Reference	Reference	Reference	Reference
2nd	1.15 (1.11–1.19), 1.5×10^{-16}	1.14 (1.10–1.17), 1.3×10^{-13}	1.07 (1.03–1.11), 0.0008	1.07 (1.03–1.11), 0.0013
3rd	1.59 (1.53–1.65), 3.5×10^{-127}	1.46 (1.40–1.52), 1.2×10^{-82}	1.19 (1.13–1.24), 3.9×10^{-13}	1.17 (1.12–1.23), 2.7×10^{-11}
4th	4.11 (3.90–4.32), $< 1.0 \times 10^{-317}$	2.11 (1.98–2.24), 2.3×10^{-119}	1.43 (1.32–1.55), 1.6×10^{-17}	1.43 (1.32–1.55), 1.1×10^{-17}
Variation				
Median odds ratio	1.89 (1.76–2.05), 5.1×10^{-11}	1.87 (1.75–2.03), 1.2×10^{-11}	1.47 (1.40–1.55), 1.5×10^{-38}	1.46 (1.39–1.55), 2.5×10^{-39}

SOI = severity of illness score.

[a]Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database dataset, 2007–2016. Cells show odds ratio (95% CI), *p* value. For median odds ratio, the parentheses include 95% credible interval.

of this study entails a possibility of measured and unmeasured confounding that can influence the interpretations. We conducted extensive sensitivity analyses to address this limitation. Our results (**Supplementary Note 2** and **Supplementary Tables 3–5**, Supplemental Digital Content 1, http://links.lww.com/CCX/A73) indicate that the influence of confounding by factors other than hypoglycemia is likely to be minimal. The unmeasured confounding factor will need to be very strongly associated with hospital mortality (OR > 4) and highly prevalent to be able to sway the association of glucose width with hospital mortality. Furthermore, a comparison of the patients in the highest and lowest quartiles of glucose width (**Supplementary Table 6**, Supplemental Digital Content 1, http://links.lww.com/CCX/A73) demonstrated very similar clinical profiles except for baseline SOI which was high in the highest quartile patients. We have therefore adjusted for this confounder in the final model. Last, the ANZICS database does not record information on all the drugs (dopamine, acetaminophen, mannitol, etc.) that have been shown (16) to influence glucose measurement. Although many of these drugs are very rarely used in the ICUs in Australia and New Zealand, the information on these drugs remains unmeasured in our study.

The mechanisms contributing to glucose variability need to be investigated in future studies. Similarly, whether glucose variability over longer duration (than 24 hr of admission studied herein) will improve prediction of hospital mortality also needs to be investigated. Finally, longitudinal studies are needed before the clinical implications of our results can be translated into practice. Nevertheless, this study demonstrates an independent association of glucose variability with hospital mortality in nonhyperglycemic ICU patients.

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