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Glycemic Variability As a Prognostic Factor for Mortality in Patients With Critical Illness: A Systematic Review and Meta-Analysis

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OBJECTIVES: To perform a systematic review and meta-analysis to evaluate the association of various measures of glycemic variability, including time-domain and complexity-domain, with short-term mortality in patients with critical illness.

DATA SOURCES: We searched Embase Classic +, MEDLINE, and the Cochrane Database of Systematic Reviews from inception to November 3, 2023.

STUDY SELECTION: We included English language studies that assessed metrics of glycemic variation or complexity and short-term mortality in patients admitted to the ICU.

DATA EXTRACTION: Two authors performed independent data abstraction and risk-of-bias assessments. We used a random-effects model to pool binary and continuous data and summarized estimates of effect using odds ratios and mean difference. We used the Quality in Prognosis Studies tool to assess risk of bias and the Grading of Recommendations, Assessment, Development and Evaluations to assess certainty of pooled estimates.

DATA SYNTHESIS: We included 41 studies ($n = 162{,}259$). We demonstrate that increased SD, coefficient of variance, glycemic lability index, and decreased time in range are probably associated with increased mortality in critically ill patients (moderate certainty) and that increased mean absolute glucose, mean amplitude of glycemic excursion, and detrended fluctuation analysis may be associated with increased mortality (low certainty).

CONCLUSIONS: We found a consistent association between increased measures of glycemic variability and higher short-term mortality in patient with critical illness. Further research should focus on standardized measurements of glycemic variation and complexity, along with their utility as therapeutic targets and prognostic markers.

KEYWORDS: critical illness; glycemic variability; prognostication

Glucose control has long been an area of interest in the management of critically ill patients admitted to the ICU. The complex interplay between stress, inflammation, and the hormonal milieu often leads to dysregulation of glucose homeostasis, resulting in hyperglycemia (1–3). Conventionally, clinical decisions are made based on point-in-time estimates of absolute glucose values. However, quantifying patterns of variability across time intervals offers novel and complementary information, which may enrich both understanding and management of glucose regulation. Accumulating evidence has demonstrated that the degree of glycemic variability (GV), which refers to fluctuations in blood glucose (BG) levels over time, is associated with patient outcomes in the ICU (1–3). Emerging data suggests that high GV may be independently associated with increased mortality and morbidity in critically ill patients, even after adjusting for

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KEY POINTS

Question: What is the association between various metrics of glycemic variability and short-term mortality in patients with critical illness?

Findings: Increased sd, coefficient of variance, glycemic lability index, and decreased time in range are probably associated with mortality in critically ill patients. Increased mean absolute glucose and mean amplitude of glycemic excursion may be associated with mortality critically ill patients. Increased detrended fluctuation analysis, which reflects decreased complexity, may be associated with mortality in critically ill patients. Additional metrics of glycemic complexity should be explored.

Meaning: We found a consistent association between all metrics of glycemic variability and short-term mortality in patient with critical illness.

mean glucose levels and the presence of diabetes (4, 5).

While the exact mechanisms linking GV to poor outcomes in the ICU remain incompletely understood, proposed explanations include increased oxidative stress, endothelial dysfunction, and activation of pro-inflammatory pathways, which could exacerbate critical illness (6). It is also possible that GV simply reflects underlying illness severity and is a marker of poor prognosis (7). The pathophysiology and the impact of GV remain an active domain of research. Despite the potential importance of GV as a prognostic factor for outcomes in critically ill patients, there is considerable heterogeneity in the methods used to measure and define GV. This heterogeneity has made it challenging to draw conclusions from individual studies and highlights the need for a systematic review, as well as a standardized approach to assessing GV.

The objective of this study was to perform a systematic review and meta-analysis summarizing the prognostic association of various measures of GV and short-term mortality in critically ill patients.

METHODS

Protocol and Registration

We used a methodology consistent with previous systematic review and meta-analysis studies addressing prognostic factors (8–10). We conducted the review in accordance with the recommendations of the PROGnosis RESearch Strategy group, the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies, and prognostic factor meta-analyses guidelines (11–16). We registered the study protocol with Open Science Framework (osf.io/w9sd4) in April 2023.

Glycemic Variability Definition

We define measures of GV broadly as any metric that characterizes glucose variation from time-series data measured over an interval-in-time. Further, we subdivide GV into: 1) time-domain glycemic variation metrics, which include measures of SD, coefficient of variance (CV), or proportion of values within target range and 2) complexity-domain measurements reflecting glycemic complexity, which quantify the degree of information (e.g., entropy or information metrics) or multiscale internal correlations (e.g., detrended fluctuation analysis [DFA]) contained within the time series. Complexity metrics generally require a larger data set for reliable assessment; however, as all metrics are derived from a time-series over an interval of time, the total number of glucose measurements (relating to the frequency and duration of measurement) may alter values and the potential domains of GV analysis performed.

Search Strategy

We devised a comprehensive search strategy that encompassed Embase Classic + Embase, MEDLINE, and Cochrane Central Register of Controlled Trials databases (**Supplemental Fig. 1**, http://links.lww.com/CCX/B288), which were searched from inception until November 3, 2023. We included English language studies with no constraints based on quality, date, or publication status. We also performed a supplemental search of Google Scholar and examined references of all included studies.

Study Selection

We included retrospective and prospective observational studies, as well as randomized controlled trials, which satisfied the following criteria: 1) adult patients (≥ 18 yr); 2) greater than or equal to 80% of the study population was admitted to an ICU; 3) reported a measure of GV (**Table 1**); and 4) evaluated an association with short-term mortality. We defined short-term mortality as ICU, in-hospital, 28-, 30-, or 90-day mortality. Where multiple time periods were available, the order of inclusion was in the order provided. We included studies if they reported adjusted odds ratio (aOR) or unadjusted odds ratio (uOR) assessing GV metrics associated with short-term mortality or reported data required to calculate mean difference or odds ratios. We attempted to contact the authors when data were missing. We excluded studies solely evaluating cardiac surgery patients as many postoperative cardiac surgery patients receive routine, uncomplicated postoperative care, and therefore, this population may have a different mortality relationship with GV. Review articles, case reports, and case series were also excluded.

Using Covidence software (Melbourne, VIC, Australia), two authors (B.N.H., J.G.) independently screened candidate citations in two stages. In the first stage, we evaluated the titles and abstracts of studies identified through the search, and any study deemed potentially eligible by either reviewer using liberal criteria underwent full-text review in the second stage. Any disagreements during full text review were resolved through discussion.

Data Abstraction and Quality Assessment

We abstracted data from each included study independently and in duplicate using a predesigned data

TABLE 1.
Definitions and Their Relationships of Terms Associated With Glycemic Variability

Metric	Definition
SD	A statistical measure of the dispersion or variation in a set of values around a mean blood glucose level. A higher SD indicates greater glycemic variability
CV	The ratio of the SD to the mean glucose level, expressed as a percentage. It standardizes the degree of variability relative to the mean, allowing for comparison across different mean glucose levels. A higher CV indicates increased glycemic variability
GLI	A measure that quantifies the rate of change of blood glucose over time by summing the squares of the difference between successive blood glucose measurements, reflecting rapid fluctuations in glucose levels. A higher GLI value signifies more rapid and frequent fluctuations in glucose levels, indicating higher glycemic variability
MAGE	A quantification of the major swings in glucose levels, both upward and downward by calculating the mean of the differences between consecutive peaks and nadirs (provided that the differences are greater than one SD from the mean glucose). A larger MAGE value indicates greater excursions or swings in glucose levels, thus higher glycemic variability
MAG	A measure of glucose dynamics that sums all absolute changes between sequential glucose measures normalized to the time interval of interest. While it is not strictly a measure of variation, it is a measure of fluctuation derived from time series data. A higher MAG is associated with higher glycemic variability
TIR	The percentage of time that a patient's blood glucose levels are within a target range. While not a direct measure of variability, it can describe overall glucose control and deviations from normal. Lower TIR can occur with both high- and low-glucose variability. High TIR is generally desirable and indicates glucose levels are well-controlled within the target range, but it does not specifically reflect glycemic variability
DFA	A statistical method used to detect correlations in time series data. In glucose monitoring, it measures the self-similarity of glucose fluctuations over time and can be used to detect patterns. A higher DFA value indicates more complex and less self-similar glucose fluctuations (i.e., higher glycemic variability)
JkApEn	A measure of the complexity and irregularity of fluctuations in time-series data, which quantifies the unpredictability of glucose fluctuations. A higher JkApEn value indicates more irregularity and unpredictability in glucose levels, representing higher glycemic variability

CV = coefficient of variance, DFA = detrended fluctuation analysis, GLI = glycemic lability index, JkApEn = jack-knifed approximate entropy, MAG = mean absolute glucose, MAGE = mean amplitude of glycemic excursion, TIR = time in range.

extraction form (**Supplemental Table 1**, http://links.lww.com/CCX/B288). We collected study characteristics including author, year, patients, and study characteristics, glucose monitoring protocol details, and GV metrics identified in univariate and multivariate analyses and their associated aOR with 95% CIs and adjustment variables, where available (**Supplemental Tables 2–4**, http://links.lww.com/CCX/B288). For studies that reported multiple measures of effect, we extracted all available data.

We evaluated risk of bias for the included studies independently and in duplicate using the Quality in Prognostic Studies tool (17). The tool was used to assess the risk of bias and its relevance to the research question in six domains, comprising study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. We resolved disagreements through discussion and third-party adjudication (A.T.). Funnel plots were constructed to evaluate for publication bias in analyses with at least five included studies.

Data Synthesis

We extracted or computed aOR, uOR, and mean difference from the available data. Glycemic lability index (GLI) measures were converted to conventional units of mmol/L/hr/wk. Similarly, we converted mg/dL to mmol/L to facilitate meta-analysis. Meta-analysis was performed using inverse variance statistics and a random-effects model, using Review Manager software (Version 5.4; Copenhagen, Denmark). We separately pooled adjusted (aOR) and unadjusted (uOR) analysis. We assessed for statistical heterogeneity (inconsistency) using the I^2 statistic, the chi-square test for homogeneity, and visual inspection of the forest plots. We performed sensitivity analyses excluding studies with periods of data collection greater than 72 hours and those examining 90-day mortality.

We used the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) methodology (18) to evaluate the certainty of pooled estimates, which were assigned as either high, moderate, low, or very low. Consistent with GRADE guidance for prognostic reviews, we considered pooled observational data as high certainty and downgraded if we identified problems in any of the GRADE domains including risk of bias, indirectness, inconsistency, and imprecision (18). Using the guideline development tool found at gradepro.org, we developed a GRADE evidence profile and used informative statements to communicate findings (a high certainty association is characterized as "is associated," moderate certainty as "probably associated," low certainty as "may be associated, and very low certainty as "uncertain association") (19).

RESULTS

Search Results

We identified 3109 citations (**Fig. 1**) in the search and included 41 eligible studies representing 162,259 patients in the final analysis (**Supplemental Tables 2–5**, http://links.lww.com/CCX/B288). The included studies reported SD (n = 25), CV (n = 22), GLI (n = 7), mean amplitude glycemic excursion (MAGE) (n = 5), mean absolute glucose (MAG) (n = 4), time in range (TIR) (n = 6), and DFA (n = 2) as metrics of GV (**Table 2**).

Risk of Bias and Quality Assessments

We judged the risk of bias in most included studies to be low in the domains of study attrition and outcome measurement. Some studies were judged to be moderate risk of bias for prognostic factor measurements for study protocols where BG sampling frequency was less than four times per day. Many studies were judged to be a moderate risk of bias for study participants in the setting of selective subgroups (i.e., specialized ICU populations). Several studies were judged to be at moderate-to-high risk of bias in adjustment and statistical reporting because of the unadjusted or mean difference data that was extracted for the purposes of our study analysis (**Supplemental Table 6**, http://links.lww.com/CCX/B288).

SD

Increased SD of BG values as a measure of GV is probably associated with increased mortality (moderate certainty) (**Supplemental Table 7**, http://links.lww.com/CCX/B288). Pooled mean difference of SD (mmol/L) was 0.51 (95% CI, 0.40–0.62) higher in those who died (5, 20–37). Pooled aOR of mortality per 1mmol/L glucose increase was 1.17 (95% CI, 1.05–1.30) and uOR was 1.03 (95% CI, 1.00–1.06) (20, 24, 32, 33, 38, 39). Pooled aOR comparing mortality in fourth vs. first

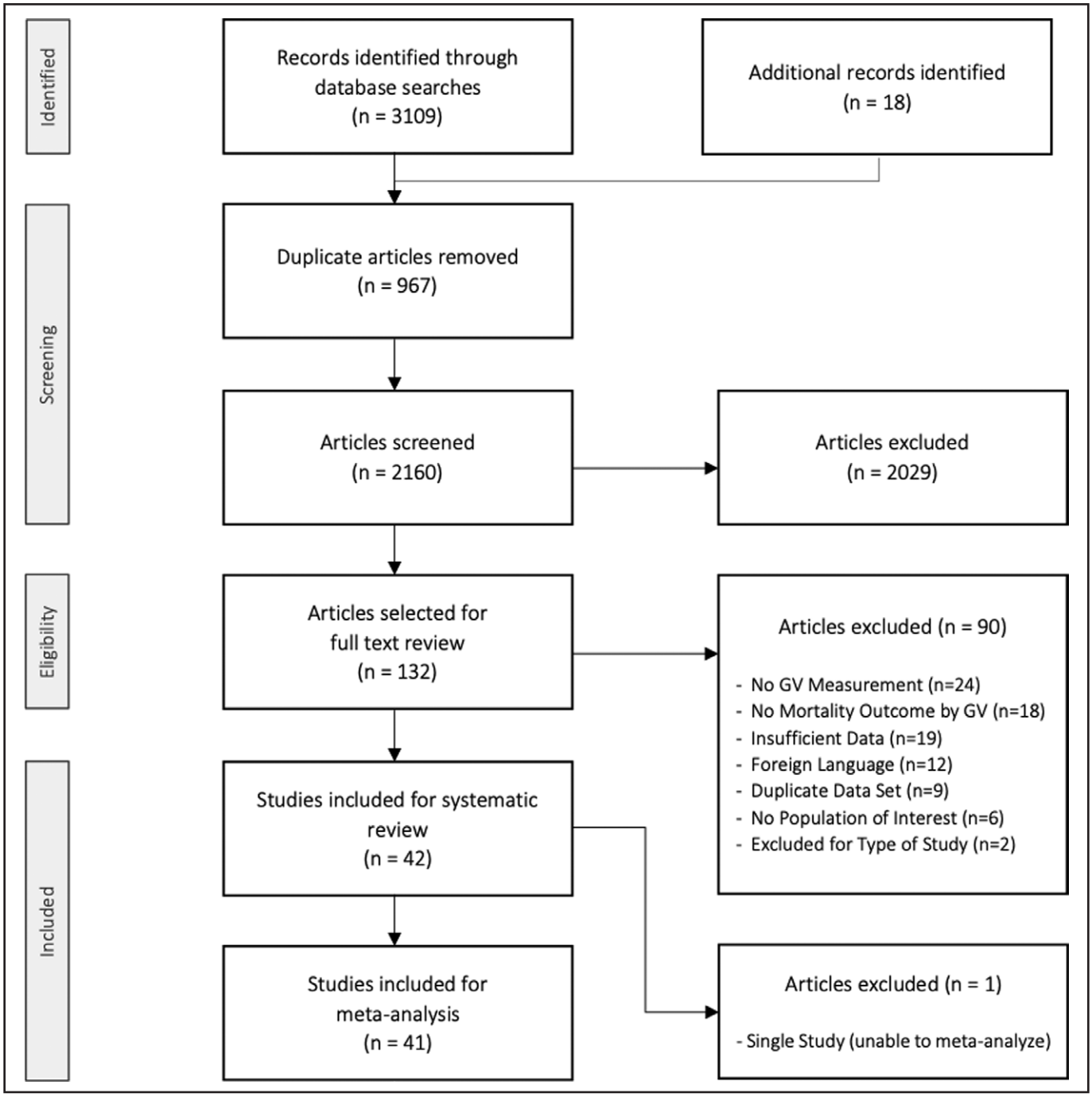

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowsheet summarizing evidence search and study selection. GV = glycemic variability.

quartile SD was 1.26 (95% CI, 0.94–1.69) and uOR was 3.60 (95% CI, 2.97–4.38) (40–43) (**Supplemental Fig. 2**, http://links.lww.com/CCX/B288).

Coefficient of Variance

Increased CV of BG values as a measure of GV is probably associated with increased mortality (moderate certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). Pooled mean difference of CV was 0.05 (95% CI, 0.04–0.07) higher in those who died (20–22, 28–36, 44, 45). Pooled aOR of mortality per 10% increase CV was 1.34 (95% CI, 1.15–1.57) (20–22, 28–36, 44, 45). Pooled aOR of mortality comparing CV above vs. below 30% was 1.79 (95% CI, 0.96–3.35) and uOR was 2.12 (95% CI, 1.77–2.53) (31, 40, 46, 47)

TABLE 2.
Meta-Analysis of Glycemic Variab ility Metrics and Association With Short-Term Mortality

Measure of Glycemic Variability		Threshold	Studies (*n*)	Effect Size	*p*	I^2	Grading of Recommendations, Assessment, Development, and Evaluations Certainty
SD							
Mean difference			19	0.51 (0.40–0.64)	$p < 0.00001$	87%	Moderate
Continuous odds ratio	aOR	Per 1 mmol/L	5	1.17 (1.05–1.30)	$p = 0.004$	78%	
	uOR		1	1.03 (1.00–1.06)	$p = 0.05$	–	
Dichotomous odds ratio	aOR	Q4 vs. Q1	1	1.26 (0.94–1.69)	$p = 0.12$	–	
	uOR		3	3.60 (2.97–4.38)	$p < 0.00001$	30%	
				Increased SD of blood glucose measurements is probably associated with short-term mortality in patients with critical illness			
Coefficient of variance							
Mean difference			14	0.05 (0.04–0.07)	$p < 0.00001$	86%	Moderate
Continuous odds ratio	aOR	Per 10% increase	8	1.34 (1.15–1.57)	$p = 0.0002$	85%	
Dichotomous odds ratio	aOR	>/< 20–30%	2	1.79 (0.96–3.35)	$p = 0.07$	76%	
	uOR		3	2.12 (1.77–2.53)	$p < 0.0001$	76%	
				Increased coefficient of variance of blood glucose measurements is probably associated with short-term mortality in patients with critical illness			
Glycemic lability index							
Mean difference			4	27.05 (20.67–33.42)	$p < 0.00001$	43%	Moderate
Continuous odds ratio	aOR	Per 1 mmol/L/hr/wk	1	2.99 (1.04–8.60)	$p = 0.04$	–	
Dichotomous odds ratio	aOR	Q4 vs. Q1	3	5.89 (1.12–30.88)	$p = 0.04$	96%	
	uOR		1	4.95 (3.09–7.93)	$p < 0.00001$	–	
				Increase glycemic lability index measurements is probably associated with short-term mortality in patients with critical illness			
Mean difference			4	0.24 (–0.23 to 0.70)	$p = 0.32$	98%	Low
Continuous odds ratio	aOR	Per 1 mmol/L/hr	1	1.04 (1.01–1.08)	$p = 0.02$	–	
Dichotomous odds ratio	aOR	Q4 vs. Q1	1	1.61 (1.01–2.56)	$p = 0.05$	–	
				Increased mean amplitude of glycemic excursion measurements may be associated with short-term mortality in patients with critical illness			

(*Continued*)

TABLE 2. (*Continued*)

Meta-Analysis of Glycemic Variab ility Metrics and Association With Short-Term Mortality

Measure of Glycemic Variability		Threshold	Studies (*n*)	Effect Size	*p*	I^2	Grading of Recommendations, Assessment, Development, and Evaluations Certainty
Mean absolute glucose							
Mean difference			1	0.06 (0.05–0.07)	$p < 0.00001$	–	Low
Continuous odds ratio	aOR	Per 1 mmol/L	1	1.00 (1.00–1.00)	$p = 0.50$	–	
Dichotomous odds ratio	aOR	Q4 vs. Q1	2	2.32 (1.21–4.47)	$p = 0.01$	81%	
				Increased mean absolute glucose measurements may be associated with short-term mortality in patients with critical illness			
Time in range							
Mean difference			1	–5.84 (–15.35 to 3.67)	$p = 0.23$	–	Moderate
Continuous odds ratio	aOR	Per 10% increase	5	0.87 (0.83–0.91)	$p < 0.00001$	18%	
Dichotomous odds ratio	aOR	>/< 80%	4	0.59 (0.53–0.65)	$p < 0.00001$	0%	
				Decreased time in range measurements is probably associated with short-term mortality in patients with critical illness			
Detrended fluctuation analysis							
Mean difference			2	0.10 (0.06–0.13)	$p < 0.00001$	50%	Low
Continuous odds ratio	aOR	Per 0.1 increase	1	2.53 (1.16–5.52)	$p = 0.02$	–	
				Increased detrended fluctuation analysis measurements may be associated with short-term mortality in patients with critical illness			

aOR = adjusted odds ratio, Q1 = first quartile, Q4 = fourth quartile, uOR = unadjusted odds ratio.
Dashes indicate data not relevant.

(**Supplemental Fig. 3**, http://links.lww.com/CCX/B288).

Glycemic Lability Index

Increased GLI as a measure of GV is probably associated with increased mortality (moderate certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). Pooled mean difference of GLI (mmol/L/hr/wk) was 27.05 (95% CI, 20.67–33.42) higher in those who died (21, 25, 26, 35). The aOR of mortality per 1 mmol/L/hr/wk increase was 2.99 (95% CI, 1.04–8.60) (33). Pooled aOR comparing mortality in fourth vs. first quartile GLI was 5.89 (95% CI, 1.12–30.88) and uOR was 4.95 (95% CI, 3.09–7.93) (21, 26, 42) (**Supplemental Fig. 4**, http://links.lww.com/CCX/B288).

Mean Amplitude of Glycemic Excursion

Increased MAGE of as a measure of GV may be associated with increased mortality (low certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). Pooled mean difference of MAGE (mmol/L) was 0.24 (95% CI, –0.23 to 0.70) higher in those who died (21, 25, 28, 37). The aOR of mortality per 1 mmol/L increase was 1.04 (95% CI, 1.01–1.08) (28). The aOR comparing mortality in fourth vs. first quartile MAGE was 1.61 (95% CI, 1.01–2.56) (46) (**Supplemental Fig. 5**, http://links.lww.com/CCX/B288).

Mean Absolute Glucose

MAG is a unique measure of glucose dynamics that sums all absolute changes between sequential glucose measures normalized to the time interval of interest (3). While this is not strictly a measure of variation, it is a measure of fluctuation derived from time series data. Increased MAG as a measure of GV may be associated with increased mortality (low certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). The mean difference of MAG (mmol/L/hr) was 0.06 (95% CI, 0.05–0.07) higher in those who died (25). The aOR of mortality per 1 mmol/L/hr increase was 1.00 (95% CI, 1.00–1.00) (48). Pooled aOR comparing mortality in fourth vs. first quartile MAG was 2.32 (95% CI, 1.21–4.47) (3, 49) (**Supplemental Fig. 6**, http://links.lww.com/CCX/B288).

Time in Range

The target range for all studies was either between 3.9 and 10.0 mmol/L or a subset within this range. Decreased TIR of BG values as a measure of GV is probably associated with increased mortality (moderate certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). The mean difference of TIR was 5.84 (95% CI, –3.67 to 15.35) higher in those who survived (25). The aOR of mortality per 10% increase TIR was 0.87 (95% CI, 0.83–0.91) (48). Pooled aOR of mortality comparing TIR above vs. below 80% was 0.59 (95% CI, 0.53–0.65) (3, 49) (**Supplemental Fig. 7**, http://links.lww.com/CCX/B288).

Glycemic Complexity

We identified three studies that reported on two distinct metrics of glycemic complexity: DFA (22, 37) and jack-knifed approximate entropy (JkApEn) (39). Analysis of JkApEn suggested that higher entropy was seen in nonsurvivors; however, no other studies have evaluated entropy of glucose variability. Two studies of glycemic DFA were included in the meta-analysis. Increased DFA of BG values, as measured with at least 48 hours of continuous glucose monitoring (CGM) data (Medtronic MiniMed, Northridge, CA), may be associated with increased mortality based on meta-analysis of mean difference (22, 37) and odds ratio of mortality per 0.1 increase in DFA (37) (low certainty) (Supplemental Table 7, http://links.lww.com/CCX/B288). Pooled mean difference of DFA was 0.10 (95% CI, 0.06–0.13) higher in those who died, where higher DFA is associated with lower complexity (for DFA above 1.0). The aOR of mortality per 0.1 increase in DFA was 2.53 (95% CI, 1.16–5.52) (**Supplemental Fig. 8**, http://links.lww.com/CCX/B288).

Funnel plots were used to evaluate for the presence of publication bias for analyses with at least five included studies (**Supplemental Fig. 9**, http://links.lww.com/CCX/B288). Sensitivity analysis was conducted for all metrics where studies with periods of data collection greater than 72 hours or 90-day mortality were excluded (**Supplemental Fig. 10**, http://links.lww.com/CCX/B288). The magnitude and CI of the estimate was impacted, but not the direction of effect.

DISCUSSION

GV studies have focused on glycemic variation metrics, which refer to the degree of dispersion from a set value or mean within a dataset of BG measurements (50). However, many variation metrics have been used including amplitude-based, such as SD, CV, GLI, and MAGE, and time-based metrics, including MAG and TIR (51). We believe this is the first systematic review and meta-analysis examining GV and the relationship to mortality in the generalized critical care population. The pragmatic approach incorporated a wide variety of protocols for BG point-of-care testing (POCT) sampling thereby allowing for an expansive and inclusive analysis. Despite some degree of unavoidable heterogeneity, using GRADE methodology we demonstrate a potential for GV as an independent predictor of short-term mortality in critically ill patients and evaluate the relative importance of various metrics of GV.

The presence of GV is likely due to the complex interplay of hormonal regulation, counter-regulatory responses, and external factors (52). In the critical care environment, it signifies a disruption in the usual tight homeostatic control of BG levels and is likely associated with an exacerbated stress response, underlying infections, or instability of the patient's condition (7, 53). Given the consistent independent association of GV to mortality after adjusting for various severity of illness scores, further consideration should be given to the incorporation of GV into existing prognostication tools for critically ill patients. Adding this unique physiologic stress dimension could improve mortality prediction score accuracy and utility in research or clinical settings. In fact, the addition of hyperglycemia, hypoglycemia, and glucose SD to the Simplified Acute Physiology Score II score has been shown to improve mortality estimates (54); however, investigation into the optimal GV metrics would be of interest. Furthermore, monitoring GV fluctuations could provide early clues about changes in a patient's physiologic condition, both to anticipate recovery as well as potential deterioration, aiding in timely therapeutic adjustments. However, more research is needed to substantiate these potential roles, particularly to better understand the likely impact of enteral and parenteral feeding and exogenous insulin administration.

It has been suggested that excessive glucose fluctuations may lead to increased oxidative stress, hormonal changes, endothelial dysfunction, and activation of pro-inflammatory pathways (1, 55–59), thereby driving an increased risk of complications and mortality. An important question, therefore, remains whether GV is simply a prognostic measure or whether it is a therapeutic target that clinicians should aim to control. While the current evidence supports the use of GV as a predictor of mortality (3, 7, 53), the therapeutic benefit of controlling GV is not clear. If efforts to control GV lead to better outcomes in critically ill patients, then interventions aimed at reducing GV could become an integral part of patient care.

While this study demonstrates a consistent association between GV and mortality through multiple metrics, there are some limitations. First, it is important to note metric-specific limitations. For example, SD does not reflect fluctuations in successive values and two patient populations could have significantly different patterns of variation but the same mean and SD. CV is inherently influenced by the mean glucose level, which may overemphasize or underemphasize GV with lower or higher mean glucose levels, respectively (60). MAGE only recognizes fluctuations greater than 1 SD and is therefore susceptible to the effects of outliers and may lack sensitivity for detecting smaller changes in glucose (61). Furthermore, while TIR is regarded as a marker of GV, there are limitations to this metric. For example, a low TIR (i.e., increased variability) could be represented by stable hyperglycemia where other metrics of variability suggest low GV. Such limitations necessitate careful interpretation of GV metrics and underscore the need for further refinement and standardization. Second, the heterogeneity in the protocols for glucose measurement period and frequency across studies may limit the accuracy of the effect size for a given GV metric. This heterogeneity may also explain minor inconsistencies for the magnitude of effect between various statistics for a given metrics. However, the largely uniform direction of effect is reassuring, and these limitations in statistical heterogeneity were accounted for in the GRADE analysis. Standardization of protocols for POCT, duration of sampling, and method of sampling might benefit future studies. Nevertheless, the findings indicate a consistent association between increased glycemic variation and higher mortality rates in critically ill patients.

CGM is an emerging technology that could offer high-resolution glucose data and be collected in

hospital through a less burdensome method for both patients and healthcare providers (62–64). Furthermore, it has been demonstrated to be reliable in the critically ill populations, including for those on vasopressors and with subcutaneous edema (65, 66). Although technically feasible to incorporate CGM into ICU management, to date, it remains rarely used. CGM systems provide high-resolution glucose data at a standardized sampling rate, allowing for enhanced variability analysis including complexity analysis of glucose time series data (63). Complexity refers to the degree of information or multiscale correlations within a time series (67). We found that decreased complexity, represented by increased DFA, was associated with mortality in critical illness. This is congruent with all other known analyses of physiologic time series (e.g., heart rate variability, respiratory rate variability, etc.) consistent with Goldberger's decomplexification theory of critical illness (68). However, in contrast, one study measured JkApEn from POCT time series data, which suggested that higher entropy may be associated with nonsurvivors (39). However, shorter time-series analyses of GV may be more reliably assessed with sample entropy (69). Still, further evaluation of glycemic complexity domains is required to understand its association with critical illness. To meet the sampling requirements for many complexity measures, CGM technology has the potential to advance our understanding of this domain of GV and the impacts on, or associations with, patient outcomes. Additionally, it offers potential avenues for real-time monitoring to allow for early intervention or feedback for tailored interventions aimed at minimizing GV, thus potentially improving patient care (70).

In conclusion, the current evidence suggests that GV is likely associated with mortality in critically ill patients across a range of critical care setting based on moderate to low certainty evidence and underscores the need for further prospective studies. Future research should aim to establish optimal and standardized methods for measuring GV in clinical practice, which may include the use of CGM to further explore GV including complexity measures. Additionally, a better understanding of glucose complexity across healthy and critically ill participants, both with and without diabetes would be of interest. Further studies to investigate the therapeutic impact of minimizing GV compared with the current standard of care for glucose control for patients with critical illness may be of future interest.

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Dr. Seely is the founder and Chief Executive Officer of Therapeutic Monitoring Systems, a company performing research, development, and commercialization of clinical decision support tools intended to improve care that uses vital sign variability and predictive modeling. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Drs. Tran and Seely are co-principal investigators and contributed equally to this study.

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