Glycaemic variability, infections and mortality in a medical–surgical intensive care unit

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ABSTRACT

Objective: In critically ill patients, glycaemic variability (GV) was reported as a better predictor of mortality than mean blood glucose level (BGL). We compared the ability of different GV indices and mean BGLs to predict mortality and intensive care unit-acquired infections in a population of ICU patients.

Design, setting and participants: Retrospective study on adult ICU patients with ⩾ three BGL measurements. GV was assessed by SD, coefficient of variation (CV) and mean amplitude of glycaemic excursion (MAGE), and by one time-weighted index, the glycaemic lability index (GLI), and compared with mean BGL. We studied 2782 patients admitted to the 12-bed medical–surgical ICU of a teaching hospital from January 2004 until December 2010.

Main outcome measures: Logistic regression analyses were performed to assess the association between GV and ICU mortality and ICU-acquired infections. The areas under receiver operating characteristic curves were calculated to compare the discriminatory ability of GV and mean BGL for infections and mortality.

Results: Mortality was 16.6%, and 30% of patients had at least one infection. Patients with infections or diabetes or who were treated with insulin had a higher mean BGL and GV than other patients. GLI, SD, CV and MAGE were significantly associated with infections and mortality; mean BGL was not. Quartiles of increasing GLI were independently associated with higher mortality and an increased infection rate. Patients in the upper quartile of mean BGL and GLI had the strongest association with infections (odds ratio, 5.044 [95% CI, 1.695–15.007]; $P = 0.004$).

Conclusion: High GV is associated with higher risk of ICU-acquired infection and mortality.

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Stress hyperglycaemia is believed to be an adaptive response to meet the increased energy demand during critical illness and to provide sufficient glucose to fuel non-insulin-dependent tissues.[1,2] Although one landmark study suggested that tight glucose control was able to reduce mortality in critically ill patients,[3] several recent multicentre randomised trials failed to provide evidence for intensive insulin therapy, which was associated with increased rates of severe hypoglycaemia[3-5] and higher 90-day mortality.[6] Hence, less strict glycaemic targets have been recommended for insulin treatment.[7-9]

The variability of blood glucose was studied and found to be a better predictor of outcome than mean blood glucose levels (BGLs) by several independent investigators.[10-15] Some researchers suggested that the lack of expected benefit from intensive insulin therapy was related to the increase in glycaemic variability (GV).[16] However, a causative link between increased GV and mortality is not established.

Hirshberg and colleagues reported large increases in the risk of nosocomial infections and mortality in a population of critically ill children with high GV, defined as blood glucose values lower and higher than the therapeutic range.[17] However, this index is not the most accurate way to assess glucose variability.[18]

Our study aimed to compare the ability of high GV (assessed by time-independent and time-weighted indices and average BGL) to predict mortality and the prevalence of infection acquired in the intensive care unit, in a mixed medical–surgical population of adult acutely ill patients.

Methods

Design

This retrospective, single-centre observational study involved adult patients consecutively admitted to the 12-bed medical–surgical ICU of a university hospital (Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona, Italy) between January 2004 and December 2010, who had at least three blood glucose measurements taken. ICU readmissions were excluded. Ethical committee consensus was not requested as this was a retrospective study.

Management of blood glucose

Blood glucose monitoring and insulin administration were managed by the nursing staff and doctors in charge, who followed the general guidelines of the department. Insulin

was given only as a continuous intravenous infusion, using a dynamic algorithm targeting a blood glucose of 4.4–8.3 mmol/L during the whole study period. According to the protocol in our ICU, an insulin infusion is usually started at blood glucose values > 8.3 mmol/L when the patient is receiving enteral or parenteral nutrition. When a value near 8.3 mmol/L is found in a fasting patient, a second measurement is performed within 30 minutes before starting insulin infusion. Blood glucose measurements included central laboratory analysis at least once a day, arterial blood samples (using GEM 4000 Premier, Instrumentation Laboratory Benelux) at least every 8 hours, or near-patient capillary tests (Hemocue B glucose analyser, Hemocue) usually every 2 hours (or more frequently in patients showing blood glucose instability).

Data collection

Data we collected from the electronic medical record (Quantitative Sentinel 5.5, Marquette Hellige, until December 2007, then Centricity Clinisoft 6.0, GE Healthcare from January 2008) included demographic data, data on the presence of diabetes, category of admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II scores,[19] blood lactate levels within the first hour of ICU admission, BGLs, data on insulin infusion during ICU stay, ICU length of stay (LOS) and microbiological test results and outcomes.

The diabetic status was defined according to the patient's medical history recorded in our electronic database, by searching for the key words: diabetes, diabetes mellitus, DM, diabetic, insulin. All results of blood, bronchoalveolar lavage, bronchial aspirate, urine, cerebrospinal fluid, wound swab and peritoneal fluid cultures were noted. We defined the presence of infection according to microbiological culture results and following the Centers for Disease Control and Prevention criteria.[20] Bacteraemia with coagulase-negative staphylococci was considered as infection whenever identical strains (compared by antibiogram) were found in peripheral and central venous blood samples.

Data analysis

All glucose values and times of glucose determinations were collected from admission to discharge from the ICU (whether the patient was alive or dead). The mean BGL for each patient was calculated from all available blood glucose values. Four indices of GV were calculated: standard deviation (SD), coefficient of variation (CV) (calculated as SD divided by mean BGL), mean amplitude of glycaemic excursion (MAGE) (calculated as the mean of absolute values of any change in mean BGL from consecutive measurements that are > one SD of the entire set of glucose values[21]) and glycaemic lability index (GLI), calculated according to the following formula:

$$\text{GLI } [(\text{mmol/L})^2/\text{h}]/\text{week} = \sum_{n=1}^{N} (\text{gluc}_n - \text{gluc}_{n+1})^2/(\text{h}_{n+1} - \text{h}_n)$$

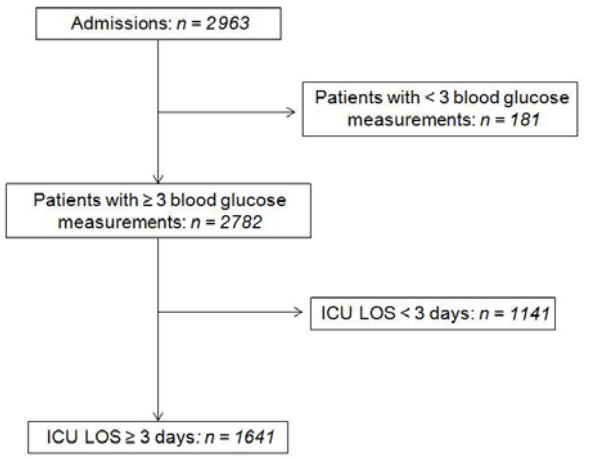
in which h = time, gluc_n (mmol/L) = the nth reading of the week taken at time h_n, and N = total number of readings in a week. The minimum and maximum time intervals used are 1 hour and 12 hours, respectively. GLI values for individual weeks were averaged for each patient.[22] For patients discharged from the ICU within 1 week after admission, GLI values were normalised on the basis of days of ICU stay.

Statistical analysis

Results are presented as medians with interquartile ranges (IQRs). The analyses were performed using SPSS, version 19.0 (SPSS Inc) and MedCalc, version 10.3.0.0 (MedCalc). Non-parametric tests (the Kruskal–Wallis test with Dunn's test, and the Mann–Whitney and χ^2 tests) were used as appropriate for comparison between patients selected for category-of-admission diagnosis, presence of infection, outcome, diabetic status and insulin infusion during ICU stay. Patients were stratified into quartiles of GLI, SD, CV and MAGE. Multivariate logistic regression models were constructed including age, APACHE II score, blood lactate level on admission, diabetic status, insulin infusion during ICU stay (as a categorical yes/no variable) and ICU LOS to calculate the adjusted odds ratios (ORs) for infections and mortality for mean BGL and each quartile of GLI, SD, CV and MAGE. The variables included in the models were selected on the basis of their reported association with outcome and/or nosocomial infections: the APACHE II score was included as a measure of illness severity; ICU LOS is a well-known risk factor for ICU-acquired infections; early blood lactate levels proved to predict the outcome better than vital signs in a prehospital setting;[23] it is well known that diabetes mellitus is associated with a higher risk of infections;[24] and insulin infusion has been suggested as a potential determinant of increased GV in ICU patients and may thus contribute to a worse outcome.[16]

The area under the receiver operating characteristic (ROC) curve was calculated to evaluate the discriminative ability of the variables towards infections and mortality for the entire cohort and for the subgroups of diabetic and non-diabetic patients. Multivariate analyses were performed separately on the entire cohort, patients with an ICU LOS of at least 3 days, and patients with and without diabetes. For a more comprehensive analysis of the interaction between glucose fluctuations and mean BGLs, patients were stratified into quartiles of mean BGL. We conducted multivariate logistic regression analysis to study the association between GV and infections for each quartile of mean BGL. Age, APACHE II score, ICU LOS,

Figure 1. Movement of patients through the study



ICU = intensive care unit. LOS = length of stay.

blood lactate level on admission, history of diabetes mellitus and insulin infusion during the ICU stay were included as covariates. A P value of < 0.05 was considered to indicate statistical significance.

Results

The movement of patients through the study is shown in Figure 1. A total of 189 317 blood glucose values were collected, and we calculated a median of 17 values/patient/day (IQR, 6–35 values/patient/day) with a median time interval of 2 hours (IQR, 1–4 hours) between readings. About 75% of blood glucose values were derived from near-patient capillary tests, 19% from arterial blood gas analyses and 6% from central laboratory determinations. General characteristics, including mean BGL, median GLI, SD and MAGE for the entire cohort, with related site and type of infection, are shown in Table 1. Most patients had mean blood glucose values within the currently recommended target; Figure 2 shows the distribution of patients along increasing ranges of mean BGL, stratified for the presence of diabetes mellitus. Figure 3 shows the distribution of patients stratified by diabetic status along increasing ranges of GV, as expressed by GLI.

Mean BGLs and the four GV indices significantly varied between groups of subjects with different categories of admission diagnosis ($P = 0.01$ for mean BGLs; $P < 0.001$ for GLI, SD, CV and MAGE), with septic patients showing the highest overall GV (Table 2).

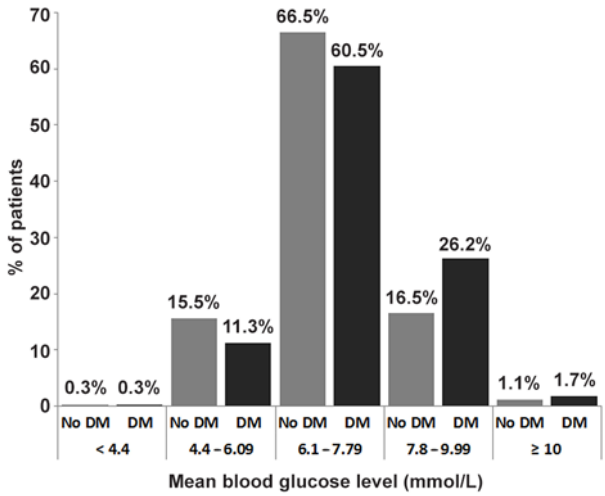
Comparisons between patients requiring and not requiring insulin infusion in ICU, between patients with

Table 1. Patient characteristics, shown as median (IQR), or as number (%) (*N* = 2782)

Characteristic	Median (IQR) or *n* (%)
Age (years)	63 (44–74)
Sex (female), *n* (%)	896 (32.2%)
Admission diagnosis, *n* (%)	
Neurological	929 (33.4%)
Postoperative	632 (22.7%)
Trauma	556 (20%)
Respiratory	278 (10%)
Sepsis	139 (5%)
Cardiac	92 (3.3%)
Other	156 (5.6%)
Blood lactate level on admission (mmol/L)	2 (1.25–3.43)
APACHE II score on admission	22 (17–28)
ICU length of stay (days)	4 (2–12)
History of diabetes mellitus, *n* (%)	303 (10.9%)
Insulin infusion in ICU, *n* (%)	1143 (41.1%)
ICU deaths, *n* (%)	462 (16.6%)
ICU infections, *n* (%)	831 (30%)
Infection source (% of total)	
Respiratory	61.5% (Enterobacteriaceae [27.6%], *Staphylococcus aureus* [23.4%], *Pseudomonas aeruginosa* [19.2%])*
Blood	24.6% (Enterobacteriaceae [24%], *P. aeruginosa* [16.6%], *S. aureus* [9.5%], *Candida* spp [10%])*
Urinary	19.9% (Enterobacteriaceae [48.9%], *Enterococcus* spp [23.1%])*
Soft tissues	8.4% (Enterobacteriaceae [25.3%], *P. aeruginosa* [22.1%], *Enterococcus* spp [12.5%], *Candida* spp [5.8%])*
Abdominal	3.6% (Enterobacteriaceae [27.5%], *Enterococcus* spp [20.7%], *Candida* spp [15.5%])*
Cerebral	2.9% (coagulase-negative staphylococci [36.6%], *P. aeruginosa* [13.3%])*
Other	6.1%
Mean blood glucose level (mmol/L)	7 (6.4–7.6)
GLI ([mmol/L]^2/hour/week)	52.56 (22–106.78)
Standard deviation (mmol/L)	1.47 (1.1–1.98)
Coefficient of variation	0.21 (0.16–0.28)
MAGE (mmol/L)	2.45 (1.79–3.38)

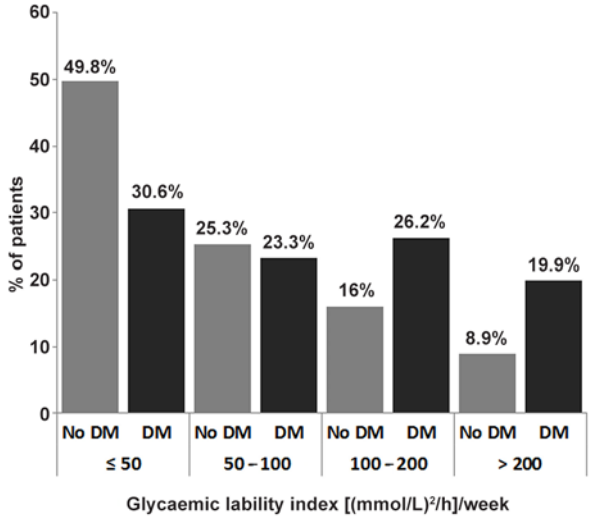
IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. GLI = glycaemic lability index. MAGE = mean amplitude of glycaemic excursion.
* Most commonly found species.

Figure 2. Distribution of patients, stratified by diabetic status and mean blood glucose level ranges



No DM = patients with no diabetes mellitus. DM = patients with diabetes.

Figure 3. Distribution of patients, stratified by diabetic status and glycaemic variability, expressed as glycaemic lability index ranges



No DM = patients with no diabetes mellitus. DM = patients with diabetes.

and without diabetes mellitus are shown in Table 3 and Table 4 respectively. Diabetic patients and those receiving an insulin infusion during their ICU stay tended to be older and more severely ill and showed higher mean BGLs and GV. Patients in the insulin subgroup showed a higher ICU mortality and a higher ICU-acquired infection incidence than those not having any insulin infusion (Table 3), but no difference in deaths or infections was found between patients with diabetes and those without (Table 4).

GV and ICU mortality

Non-survivors were older and had higher APACHE II scores and blood lactate levels on admission compared with survivors, and a higher percentage of patients in the non-survivor group had an insulin infusion during their ICU stay. All the studied GV indices were significantly higher in non-survivors than in survivors, while no differences were found for mean BGLs (Table 5).

ROC curve analysis showed that all indices of GV were weak but significant predictors of mortality, unlike mean

Table 2. Comparison of mean blood glucose levels and glycaemic variability, by admission diagnosis (data are medians [interquartile ranges])

Admission diagnosis	Mean blood glucose level (mmol/L)	Glycaemic lability index ([mmol/L]^2/hour/week)	Standard deviation (mmol/L)	Coefficient of variation	Mean amplitude of glycaemic excursion (mmol/L)
Neurological	7 (6.5–7.6)[a]**	59.1 (26–109.1)[b]**,[a]***	1.5 (1.1–1.9)[b]*	0.21 (0.17–0.27)[b]**	2.5 (1.8–3.3)[b]**
Postoperative	70 (6.4–7.7)	44.8 (16.1–100.8)	1.4 (0.9–1.9)	0.2 (0.14–0.27)	2.3 (1.5–3.2)
Trauma	6.8 (6.3–7.4)	40.9 (20.1–81.5)	1.4 (1.1–1.9)	0.2 (0.17–0.27)	2.3 (1.8–3.2)
Respiratory	6.9 (6.5–7.5)	52.9 (23.8–106.9)	1.5 (1.2–2)[c]**	0.23 (0.17–0.29)[c]***	2.7 (1.9–3.4)[c]***
Sepsis	6.9 (7.4–7.7)	91.4 (43.9–166.9)[d]***,[e]***,[f]***,[g]***	1.8 (1.3–2.3)[d]***,[e]***,[f]***	0.24 (0.19–0.3)[d]*,[e]***,[f]**	2.9 (2.2–4)[d]**,[e]***,[f]**
Cardiac	7.2 (6.3–7.7)	65.9 (35.4–129.6)[h]**,[i]*	1.6 (1.1–2.2)[h]*	0.23 (0.17–0.3)[h]*	2.8 (1.8–3.8)
Other	7.2 (6.5–7.8)[j]*	68.7 (27.4–134.4)[j]**,[k]**	1.6 (1.1–2.2)	0.22 (0.16–0.28)	2.6 (1.8–3.7)[k]**

a = neurological v postoperative. b = neurological v trauma. c = postoperative v respiratory. d = neurological v sepsis. e = postoperative v sepsis. f = trauma v sepsis. g = respiratory v sepsis. h = postoperative v cardiac. i = trauma v cardiac. j = trauma v other. k = postoperative v other. Kruskal-Wallis test with Dunn's test used: * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

Table 3. Comparison between patients, by insulin infusion requirement during ICU stay

Patient characteristic	Insulin	No insulin
Patients, *n* (%)	1143 (41%)	1639 (59%)
Median age, years (IQR)	65 (49–74)***	58 (36–73)
Median blood lactate level on admission, mmol/L (IQR)	2.1 (1.3–3.6)**	1.9 (1.2–3.3)
Median APACHE II score on admission (IQR)	24 (19–29)***	21 (16–27)
Median ICU LOS, days (IQR)	8.7 (3.7–17.5)***	3.8 (1.8–7.9)
History of diabetes mellitus, *n* (%)	185 (16.2%)###	117 (7.1%)
ICU deaths, *n* (%)	258 (22.6%)###	223 (13.6%)
ICU-acquired infections, *n* (%)	518 (45.3%)###	347 (21.2%)
Median BGL, mmol/L (IQR)	7.1 (6.6–7.6)***	6.9 (6.3–7.5)
Median GLI, $(mmol/L)^2$/h/week (IQR)	78.5 (41.9–137.2)***	36.4 (15.6–81)
Median SD, mmol/L (IQR)	1.6 (1.2–2.1)***	1.3 (1–1.9)
Median CV (IQR)	0.23 (0.18–0.29)***	0.2(0.15–0.27)
Median MAGE, mmol/L (IQR)	2.7 (2.1–3.6)***	2.3 (1.6–3.2)

ICU = intensive care unit. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. LOS = length of stay. BGL = blood glucose level. GLI = glycaemic lability index. SD = standard deviation. CV = coefficient of variation. MAGE = mean amplitude of glycaemic excursion. ** $P < 0.01$, Mann–Whitney test. *** $P < 0.001$, Mann–Whitney test. ### $P < 0.001$, χ^2 test.

Table 4. Comparison between patients, by presence of diabetes mellitus

Patient characteristic	Diabetes	No diabetes
Patients, *n* (%)	303 (10.9%)	2479 (89.1%)
Median age, years (IQR)	69 (62–76)***	60 (41–73)
Median blood lactate level on admission, mmol/L (IQR)	1.85 (1.2–3.4)	2 (1.2–3.4)
Median APACHE II score on admission (IQR)	24 (19–28)***	22 (17–28)
Median ICU LOS, days (IQR)	4.7 (2–14.2)	5.7 (2.6–13)
ICU insulin infusion, *n* (%)	185 (61%)###	958 (38.6%)
ICU deaths, *n* (%)	57 (19%)	426 (17.2%)
ICU-acquired infections, *n* (%)	100 (33.2%)	776 (31.3%)
Median BGL, mmol/L (IQR)	7.2 (6.6–8)***	6.9 (6.4–7.6)
Median GLI, $(mmol/L)^2$/h/week (IQR)	90.3 (40.8–171.1)***	50.3 (21–99.3)
Median SD, mmol/L (IQR)	1.7 (1.2–2.4)***	1.4 (1.1–1.9)
Median CV (IQR)	0.24 (0.18–0.32)***	0.21 (0.16–0.27)
Median MAGE, mmol/L (IQR)	2.8 (2–4)***	2.4 (1.8–3.3)

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. LOS = length of stay. BGL = blood glucose level. GLI = glycaemic lability index. SD = standard deviation. CV = coefficient of variation. MAGE = mean amplitude of glycaemic excursion. *** $P < 0.001$, Mann–Whitney test. ### $P < 0.001$, χ^2 test.

BGLs (Figure 4). The discriminative ability for mortality was not different between GLI, CV, SD and MAGE.

Multivariable logistic regression analysis, besides demonstrating an association between ICU mortality and APACHE II score (OR, 1.12 per unit change [95% CI, 1.10–1.14]; $P < 0.001$), blood lactate on admission (OR, 1.011 per unit increase [95% CI, 1.006–1.016]; $P < 0.001$) and insulin infusion during ICU stay (OR, 1.369 [95% CI, 1.061–1.766]; $P = 0.016$), showed that the risk of death progressively increased by quartiles of GLI, in the entire cohort and in the subgroup of patients with ICU LOS $\geqslant 3$ days (Table 6). On the contrary, no significant association was found between mortality and diabetic status, mean BGL, SD, CV or MAGE.

GV and ICU-acquired infections

Patients with infections had significantly longer ICU LOSs, higher APACHE II scores, a greater need for insulin infusion during their ICU stay, showed more severe GV, but their mean BGLs were similar to those of patients without infections (Table 7).

All the studied GV indices were significantly associated with infections, with GLI showing a higher discriminative ability compared with MAGE ($P = 0.04$) and SD ($P = 0.02$) but not CV (Figure 5).

In the multivariate logistic regression analysis, ICU LOS (OR, 1.098 [95% CI, 1.085–1.112], $P < 0.001$), APACHE II score (OR, 1.029 [95% CI, 1.015–1.044], $P < 0.001$) and insulin infusion during ICU stay (OR, 1.443 [95% CI, 1.162–1.793], $P = 0.001$) were independently associated with ICU-acquired infections. The strength of the association between infections and GLI increased progressively by quartile of GLI either in the entire cohort and in patients with an ICU LOS $\geqslant 3$ days (Table 8). No association was found with diabetic status, mean BGL, SD, CV or MAGE.

After stratifying patients into quartiles of mean BGL, the incidence of infections was calculated for each quartile of GLI within categories of mean BGL (Figure 6 and Figure 7).

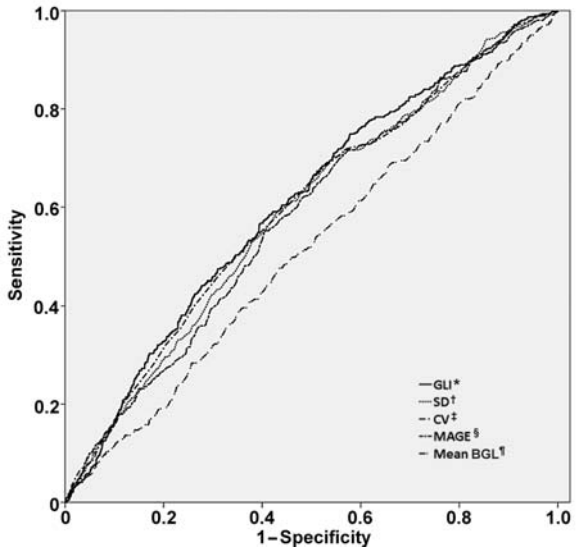
No symmetrical trend of increasing incidence of infections and quartile of mean BGL was seen. In the multivariate logistic regression analysis performed for each quartile of mean BGL, patients in the third and fourth quartiles showed an increasing chance of having a diagnosis of infection with increasing quartiles of GLI. The highest incidence of infections was seen among patients in the upper quartile of both mean BGL and GLI (Table 8).

Table 5. Comparison between ICU non-survivors and survivors, by univariate analysis

Patient characteristic	ICU non-survivors	ICU survivors
Patients, *n* (%)	462 (16.6%)	2320 (83.4%)
Median age, years (IQR)	68 (51–76)***	62 (42–73)
History of diabetes mellitus, *n* (%)	56 (12.1%)	239 (10.3%)
Insulin infusion during ICU stay, *n* (%)	255 (55.2%)###	875 (37.7%)
Median APACHE II score on admission (IQR)	28 (23–32)***	21 (16–26)
ICU LOS, days (IQR)	5 (2–13)*	4 (2–12)
Median blood lactate level on admission, mmol/L (IQR)	2.7 (1.6–5)***	1.9 (1.2–3.2)
Presence of infection, *n* (%)	215 (46.5%)###	615 (26.5%)
Median BGL, mmol/L (IQR)	7 (6.4–7.6)	7 (6.4–7.6)
Median GLI, $(mmol/L)^2/h/week$ (IQR)	75.6 (37.9–148.4)***	50.1 (21.1–99.6)
Median CV (IQR)	0.23 (0.17–0.3)***	0.21 (0.16–0.27)
Median SD, mmol/L (IQR)	1.7 (1.2–2.2)***	1.4 (1.1–1.9)
Median MAGE, mmol/L (IQR)	2.7 (2–3.7)***	2.4 (1.8–3.3)

ICU = intensive care unit. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. LOS = length of stay. BGL = blood glucose level. GLI = glycaemic lability index. CV = coefficient of variation. SD = standard deviation. MAGE = mean amplitude of glycaemic excursion. * $P < 0.05$, Mann–Whitney test. *** $P < 0.001$, Mann–Whitney test. ### $P < 0.001$, χ^2 test.

Figure 4. Receiver operating characteristic curves of GLI, SD, CV, MAGE and mean BGL, for ICU mortality in entire cohort (*n* = 2782)



GLI = glycaemic lability index. CV = coefficient of variation. MAGE = mean amplitude of glycaemic excursion. BGL = blood glucose level. ICU = intensive care unit. * GLI: AUC, 0.61; 95% CI, 0.58–0.64; $P < 0.001$. † SD: AUC, 0.59; 95% CI, 0.56–0.63; $P < 0.001$. ‡ CV: AUC, 0.60; 95% CI, 0.58–0.62; $P < 0.001$. § MAGE: AUC, 0.59; 95% CI, 0.56–0.62; $P < 0.001$. ¶ Mean BGL: $P < 0.05$. Discriminative ability for mortality was not different between GLI, CV, SD and MAGE.

GV, mortality and infections in patients with diabetes versus those without

In patients with no history of diabetes mellitus, GV was significantly associated with ICU mortality and ICU-acquired infections, as expressed by the increasing risk of death and infection with increasing quartiles of GLI. On the contrary, no relation was found between GV and ICU mortality in patients with diabetes. A significant association was seen in these patients between quartiles of GLI and ICU-acquired infections (Table 7).

ROC curve analysis restricted to patients with no history of diabetes showed a weak but significant discriminative ability for ICU mortality, for the four GV indices (GLI: area under the curve [AUC], 0.62 [95% CI, 0.59–0.65], $P<0.001$; SD: AUC, 0.60 [95% CI,

Table 6. Comparison between patients with and without infections, by univariate analysis

Patient characteristic	Infection	No infection
Patients, *n* (%)	834 (30%)	1952 (60%)
Median age, years (IQR)	63 (45–74)	63 (43–74)
History of diabetes mellitus, *n* (%)	98 (11.8%)	197 (10.1%)
Insulin infusion during ICU stay, *n* (%)	511 (61.3%)###	617 (31.6%)
Median APACHE II score on admission (IQR)	24 (19–29)***	21 (16–27)
ICU LOS, days (IQR)	13 (5.6–24.2)***	3 (1.7–6.1)
Median blood lactate level on admission, mmol/L (IQR)	2.1 (1.3–3.6)	2 (1.2–3.4)
ICU deaths, *n* (%)	215 (25.8%)###	247 (12.7%)
Median BGL, mmol/L (IQR)	7 (6.5–7.5)	7 (6.4–7.6)
Median GLI, $(mmol/L)^2/h/week$ (IQR)	73.5 (38.8–130.4)***	44.6 (18.4–95.6)
Median CV (IQR)	0.23 (0.18–0.29)***	0.2 (0.15–0.27)
Median SD, mmol/L (IQR)	1.6 (1.3–2.1)***	1.4 (1–1.9)
Median MAGE, mmol/L (IQR)	2.7 (2.1–3.6)***	2.3 (1.7–3.2)

IQR = interquartile range. ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. LOS = length of stay. BGL = blood glucose level. GLI = glycaemic lability index. CV = coefficient of variation. SD = standard deviation. MAGE = mean amplitude of glycaemic excursion. *** $P < 0.001$, Mann–Whitney test. ### $P < 0.001$, χ^2 test.

Table 7. Adjusted ORs (95% CI) for ICU mortality and infections in the entire cohort, patients with ICU LOS ⩾ 3 days, diabetic and non-diabetic patients, by GLI quartile*

Patient quartile of GLI ([mmol/L]^2/hour/week)	ICU mortality, OR (95% CI)	*P*	ICU-acquired infections, OR (95% CI)	*P*
All patients (*n* = 2782)				
GLI quartile 1 (< 22)	Reference	*P* for trend = 0.009	Reference	*P* for trend < 0.001
GLI quartile 2 (22–52.5)	1.217 (0.815–1.816)	0.337	1.657 (1.200–2.287)	0.002
GLI quartile 3 (52.6–106.7)	1.447 (0.976–2.144)	0.066	1.760 (1.270–2.439)	0.001
GLI quartile 4 (> 106.7)	1.851 (1.257–2.726)	0.002	2.271 (1.635–3.155)	< 0.001
ICU LOS ⩾ 3 days (*n* = 1641)				
GLI quartile 1 (< 29.1)	Reference	*P* for trend < 0.001	Reference	*P* for trend < 0.001
GLI quartile 2 (29.1–58.7)	1.573 (1.012–2.446)	0.044	1.451 (1.048–2.010)	0.025
GLI quartile 3 (58.7–111.4)	2.038 (1.318–3.153)	0.001	1.740 (1.253–2.416)	0.001
GLI quartile 4 (> 111.4)	3.025 (1.915–4.778)	< 0.001	2.129 (1.530–2.961)	< 0.001
Non-diabetic (*n* = 2479)				
GLI quartile 1 (< 21)	Reference	*P* for trend = 0.001	Reference	*P* for trend = 0.002
GLI quartile 2 (21–50.3)	1.311 (0.847–2.030)	0.224	1.550 (1.099–2.188)	0.013
GLI quartile 3 (50.3–99.3)	1.463 (0.947–2.260)	0.087	1.605 (1.132–2.277)	0.008
GLI quartile 4 (> 99.3)	2.188 (1.434–3.337)	< 0.001	1.982 (1.393–2.822)	< 0.001
Diabetic (*n* = 303)				
GLI quartile 1 (< 40.4)	Reference	NS	Reference	*P* for trend = 0.002
GLI quartile 2 (40.4–90.3)	3.921 (1.071–14.335)	NS	3.375 (1.181–9.642)	0.023
GLI quartile 3 (90.3–169.2)	2.440 (0.506–11.759)	NS	6.430 (2.274–18.179)	< 0.001
GLI quartile 4 (> 169.2)	3.174 (0.589–17.110)	NS	6.286 (2.254–17.532)	< 0.001

OR = odds ratio. ICU = intensive care unit. LOS = length of stay. GLI = glycaemic lability index. NS = not significant. * Variables included in multivariate regression model were age, Acute Physiology and Chronic Health Evaluation II score, ICU LOS, blood lactate level on admission, history of diabetes mellitus, insulin infusion during ICU stay (as categorical yes/no variable), mean blood glucose level, GLI quartiles, SD quartiles, coefficient of variation quartiles and mean amplitude of glycaemic excursion quartiles (history of diabetes mellitus was excluded for the subgroup analyses of non-diabetic and diabetic patients).

0.57–0.63], $P<0.001$; CV: AUC, 0.61 [95% CI, 0.58–0.64], $P<0.001$; MAGE: AUC, 0.59 [95% CI, 0.59–0.62], $P<0.001$). On the contrary, none of the four indices was predictive of ICU mortality in the subgroup of diabetic patients.

GLI, SD, CV and MAGE all carried a significant association with ICU-acquired infections in non-diabetic patients (GLI: AUC, 0.62 [95% CI, 0.59–0.64], $P<0.001$; SD: AUC, 0.60 [95% CI, 0.57–0.62], $P<0.001$; CV: AUC, 0.60 [95% CI, 0.58–0.63], $P<0.001$; MAGE: AUC, 0.60 [95% CI, 0.58–0.62], $P<0.001$) and in diabetic patients (GLI: AUC, 0.66 [95% CI, 0.60–0.72], $P<0.001$; SD: AUC, 0.62 [95% CI, 0.55–0.68], $P=0.001$; CV: AUC, 0.62 [95% CI, 0.55–0.68], $P=0.001$; MAGE: AUC, 0.63 [95% CI, 0.57–0.70], $P<0.001$).

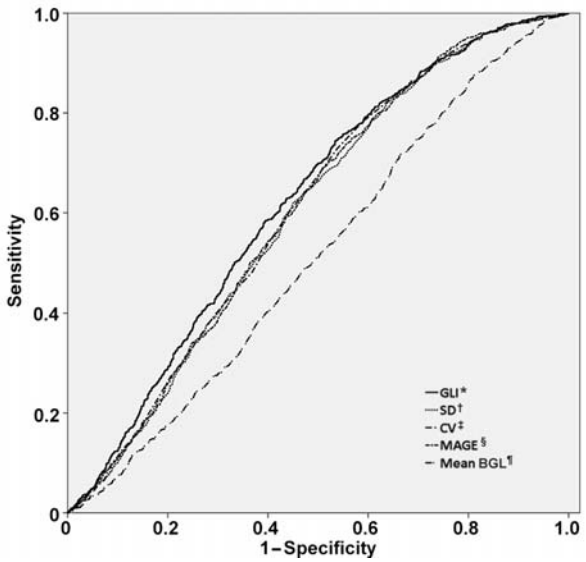
Mean BGL did not show any discriminative ability for ICU mortality or association with infections in non-diabetic or diabetic patients.

Discussion

In our retrospective study of a mixed population of adult critical patients, GV was independently associated with higher ICU mortality and rate of ICU-acquired infections, even after adjustment for potential confounders.

The association between high GV and mortality has already been shown in different populations of ICU patients, although the precise mechanism of toxicity has not been identified.[10-16] An association between increased GV and increased rate of infection has only been reported in a paediatric population.[17] A connection between chronic hyperglycaemia and increased risk of infection is well known in patients with poorly controlled diabetes, in whom some mechanisms of immune dysregulation have been shown.[24] In acutely ill patients, the potential mechanisms linking hyperglycaemia or GV and infections is mostly unknown but could be related to functional alterations of the immune system, including an enhanced glucose uptake by macrophages and granulocytes,[25] changes in the polymorphonuclear respiratory burst,[26] or the release of inflammatory mediators.[27] Another explanation is that infection or its development can induce glycaemic instability, which would then be a consequence rather than a cause of infection. Our finding of higher GV among septic patients would be consistent with this assumption.

Figure 5. Receiver operating characteristic curves of GLI, SD, CV, MAGE and mean BGL, for ICU-acquired infections in entire cohort (*n* = 2782)



GLI = glycaemic lability index. CV = coefficient of variation. MAGE = mean amplitude of glycaemic excursion. BGL = blood glucose level. ICU = intensive care unit. AUC = area under the curve. * GLI: AUC, 0.62; 95% CI, 0.60–0.64; $P < 0.001$. † SD: AUC, 0.60; 95% CI, 0.58–0.62; $P < 0.001$. ‡ CV: AUC, 0.61; 95% CI, 0.59–0.63; $P < 0.001$. § MAGE: AUC, 0.60; 95% CI, 0.58–0.62; $P < 0.001$. ¶ Mean BGL: AUC, 0.53; 95% CI, 0.50–0.55; $P = 0.036$. GLI was a better predictor of ICU-acquired infection than MAGE, SD or mean BGL.

We found a weak but significant (AUC, 0.6) non-linear relationship between GV and ICU-acquired infections. Among the studied indices of GV, GLI was more strongly associated with infections than SD, CV or MAGE. The superiority of GLI in predicting outcome compared with SD and MAGE have been previously reported.[18] In contrast to GLI, neither SD nor MAGE take into account the time intervals between measurements;[28] MAGE does not discern the number of excursions, and in the hypothetical situation in which only one major decline or rise had occurred, a high MAGE reading would follow.[22] These indices were designed for long-term monitoring of patients with diabetes, a different scenario to that of acute illness. Consequently, it is logical to assume that ICU LOS, as well as increasing the risk of nosocomial infections, might have influenced the calculation of GV indices, leading, for example, to lower SD values for patients with a longer ICU LOS and a larger number of blood glucose measurements than patients who have a short ICU LOS. Despite this, ICU-acquired infections proved to be associated with higher GVs and longer ICU LOSs.

Table 8. Adjusted ORs (95% CI) for ICU infection per GLI quartile, stratified by mean BGL quartile*

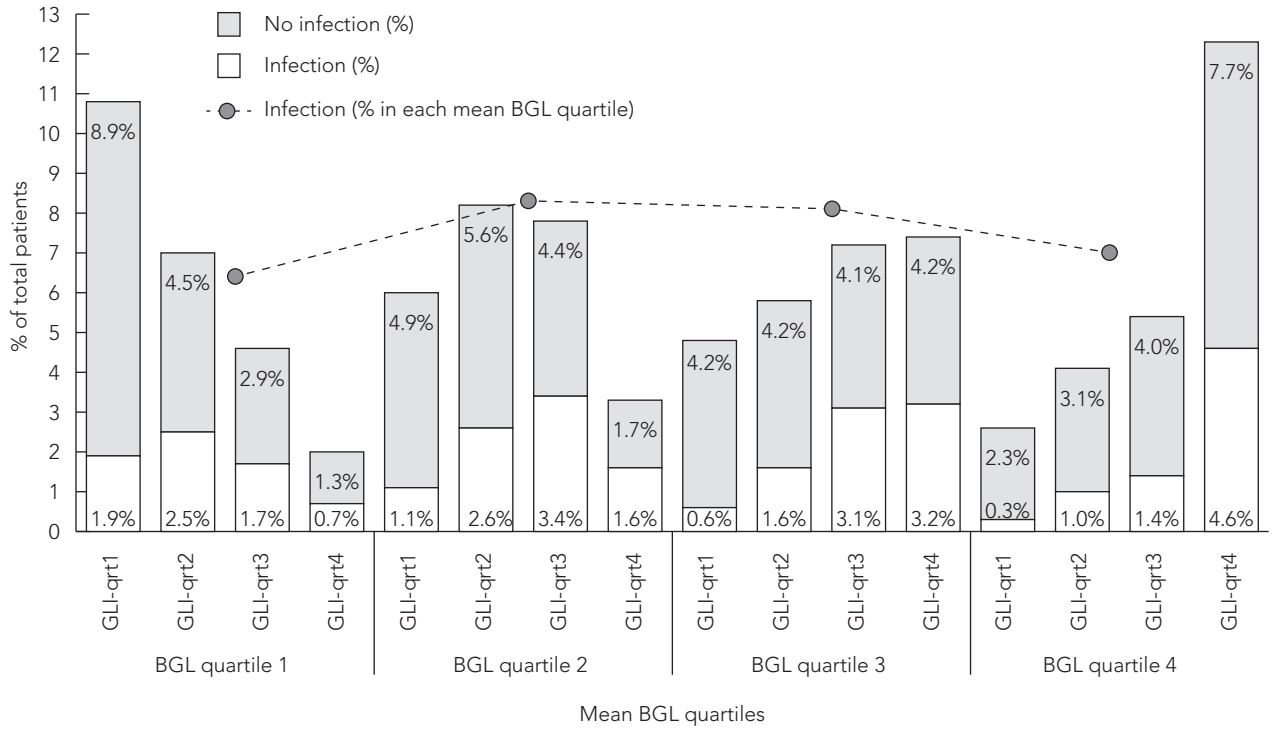
Mean BGL quartile	ICU infection, OR (95% CI)	*P*
Mean BGL Q1 (< 6.4)†		
GLI Q1 (< 22)‡	Reference	*P* for trend = 0.018
GLI Q2 (22–52.5)‡	2.175 (1.305–3.624)	0.003
GLI Q3 (52.6–106.7)‡	1.512 (0.834–2.741)	0.173
GLI Q4 (> 106.7)‡	2.202 (1.016–4.772)	0.045
Mean BGL Q2 (6.4–6.9)†		
GLI Q1 (< 22)‡	Reference	NS
GLI Q2 (22–52.5)‡	0.723 (0.389–1.343)	NS
GLI Q3 (52.6–106.7)‡	1.075 (0.527–2.194)	NS
GLI Q4 (> 106.7)‡	1.285 (0.513–3.216)	NS
Mean BGL Q3 (7–7.6)†		
GLI Q1 (< 22)‡	Reference	*P* for trend = 0.046
GLI Q2 (22–52.5)‡	1.594 (0.716–3.548)	0.254
GLI Q3 (52.6–106.7)‡	2.416 (1.094–5.336)	0.029
GLI Q4 (> 106.7)‡	2.991 (1.278–6.999)	0.012
Mean BGL Q4 (> 7.6)†		
GLI Q1 (< 22)‡	Reference	*P* for trend = 0.009
GLI Q2 (22–52.5)‡	3.182 (0.990–10.227)	0.052
GLI Q3 (52.6–106.7)‡	3.201 (1.026–9.991)	0.045
GLI Q4 (> 106.7)‡	5.044 (1.695–15.007)	0.004

OR = odds ratio. ICU = intensive care unit. GLI = glycaemic lability index. BGL = blood glucose level. Q = quartile. NS = not significant. * Variables included in multivariate regression model were age, Acute Physiology and Chronic Health Evaluation II score, ICU length of stay, blood lactate level on admission, history of diabetes mellitus, insulin infusion during ICU stay (as categorical yes/no variable), GLI quartiles, SD quartiles, coefficient of variation quartiles and mean amplitude of glycaemic excursion quartiles. GLI and mean BGL quartiles are calculated for the entire cohort. Logistic regression analysis was performed for each quartile of mean BGL separately. † mmol/L. ‡ $(mmol/L)^2/h/week$.

Mean BGL was not associated with infections or found to be a predictor of mortality, thus apparently contradicting a previous study by our group on a different population.[29] This discrepancy can explained by the substantial lowering of mean BGLs due to changes in BGL management protocols. The previous cut-off value of 7.9 mmol/L was not achieved in 80% of the patients in our study. Similarly, the observed BGLs may not have been high enough to lead to an increased risk of infection.

However, hyperglycaemia might still have played a role. Recent studies have repeatedly highlighted an important interaction between mean BGLs and GV in increasing the risk of mortality.[12,13,16] This interaction may also determine the risk of ICU-acquired infection, which appeared to rise dramatically in our population when increasing variability was accompanied

Figure 6. Distribution of patients with and without infections, by quartile of mean BGL,* substratified by quartile of GLI



BGL = blood glucose level. GLI = glycaemic lability index. GLI-qrt = GLI quartile. * Each quartile of mean BGL contained about 690 patients. Percentages in each column are percentages of the entire cohort. Dotted line shows overall incidence of infections within each quartile of mean BGL.

by high BGLs. Patients in the upper GLI category and the highest quartile of mean BGL showed a higher adjusted OR than those with similar GV but lower mean BGLs. However, we cannot exclude the possibility that the infection induced the changes in BGL, rather than being the consequence of glucose instability.

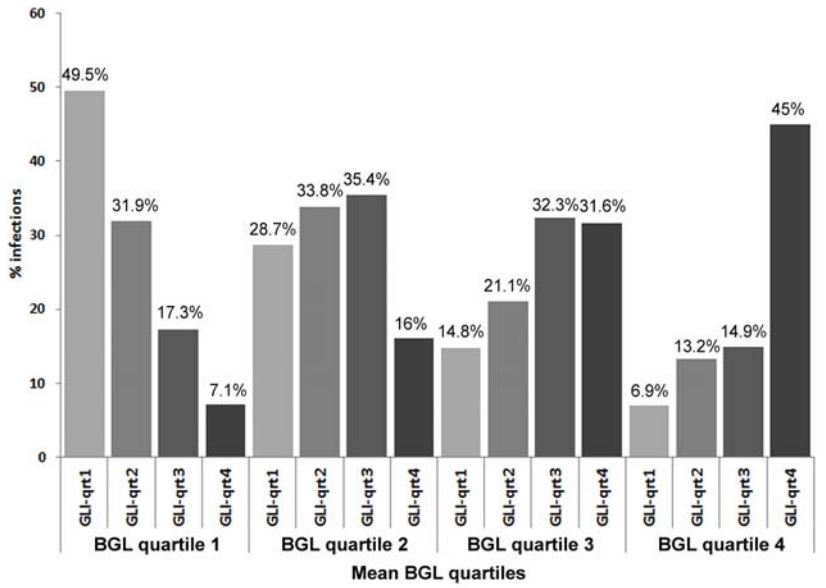
Recent studies suggest that the association between dysglycaemia and clinical outcome variables might be weaker in critically ill diabetic patients.[30,31] Our results are consistent with these findings. Despite higher mean BGL and more severe GV among patients with diabetes mellitus, there was no increase in mortality or the rate of infection. On the other hand, the association between GV and infections was also found among diabetic patients, with those in the upper quartiles of GLI showing a sixfold higher risk for ICU-acquired infections than those in the lowest GLI quartile. However, given the lack of any significant difference in the number of ICU-acquired infections between diabetic and non-diabetic patients, despite the higher GV among diabetic patients, one could suppose that larger BGL fluctuations are needed to increase susceptibility to nosocomial infections in patients with diabetes.

However, the fact remains that "association" does not mean "causality" and any speculation about the impact of reducing GV on the risk of nosocomial infections would go beyond the intrinsic limitations of our retrospective study. Only prospective randomised trials could really clarify whether reducing GV may prevent the onset of infections and what targets for glucose management would be appropriate for critically ill patients with or without diabetes.[32]

Lastly, we found an association between insulin infusion and increased risk of mortality and infections. This would support the theory that intensive insulin therapy, with the aim of preventing hyperglycaemia, may cause excessive lowering of BGL and increase GV.[16] However, patients needing insulin infusion in our cohort were also more severely ill (with higher APACHE II scores and blood lactate levels on admission, and longer ICU LOSs). Therefore, the association may be just an epiphenomenon of a more severe glucose control alteration in patients who required insulin infusion.

Our study has several limitations. First, its retrospective nature does not allow clarification of the real cause–effect relationship underlying the association between GV, mortal-

Figure 7. Distribution of patients with infections, by quartile of mean BGL,* substratified by quartile of GLI



GLI = glycaemic lability index. GLI-qrt = GLI quartile. BGL = blood glucose level. * Each quartile of BGL contained about 690 patients. Percentages in each column refer to each GLI quartile.

ity and ICU-acquired infections. Unfortunately, it was not possible to ascertain whether GV preceded or was a consequence of the infection, since our database did not allow us to obtain information on the day of infection occurrence. The heterogeneous nature of the population (with patient-related confounders such as disease severity, age and type of admission) is likely to minimise the strength of statistical associations.

Another limitation is the intermittent BGL monitoring, the frequency of which varied from one patient to another, thereby influencing the estimation of GV. Less frequent measurements in less severely ill patients might reduce the apparent frequency and extent of deviations. Our glucose values originated from different methods of measurement, including point-of-care glucose meters, which have higher degrees of error compared with laboratory serum values.[33,34] This variation might have contributed to increased GV. Only continuous blood glucose monitoring would overcome these limitations and allow discrimination between pathological variability and physiological complexity, ie, the spontaneous homoeostatic irregularity in blood glucose which seemed to be lost in patients with a worse outcome.[35]

Infections were retrospectively identified on the basis of positive cultures recorded in our electronic database and we cannot be sure we excluded all possible contaminations and may have missed clinically suspected infections with negative culture reports. Our electronic medical record does not provide information about the days of mechanical ventilation, which is a well known risk factor for lower airway infections, and a possible source of bias.

Other potential confounders, such as steroid therapy, the type of nutritional support, insulin doses (which can influence glucose regulation and contribute to its variability[36]) and the use of antibiotics, could not be evaluated. Furthermore, we cannot exclude the possibility that we missed the presence of diabetes in some patients whose recorded medical history may have been incomplete; the percentage of diabetic patients (10%) in our cohort seems low compared with that of other mixed ICU populations described in the literature.[30] We did not consider the relationship between infections and hypoglycaemia, which is the third aspect of glucose dysmetabolism associated with a higher ICU mortality.[37] However, our analysis focused on the potential harmful effect of acute GV rather than mean BGLs.

Our study demonstrates that GV is independently associated with ICU mortality and ICU-acquired infections in a mixed population of critically ill adult patients. GV is associated with infections but not ICU mortality in patients with diabetes mellitus. Further studies should clarify the cause–effect relationships.

Competing interests

None declared.

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