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Original Article

# Diabetic status and the relationship of blood glucose to mortality in adults with carbapenem-resistant *Acinetobacter baumannii* complex bacteremia



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## KEYWORDS

*Acinetobacter baumannii* complex;  
Diabetes;  
Glycemic variability

**Abstract** *Background/Purpose:* Diabetes is associated with increased mortality in *Acinetobacter baumannii* (AB) complex infection. This study investigated the risk factors and relationship of diabetic status and glycemic indices to mortality in patients with carbapenem-resistant (CR) AB complex bacteremia.

*Methods:* Relationship of glycemic indices to mortality were compared in adult diabetes (DM) and nondiabetes (non-DM) patients with CRAB complex bacteremia hospitalized from January 2010 to December 2015 in MacKay Memorial Hospital, Taiwan.

*Results:* Of 317 patients with CRAB complex bacteremia, 146 (46.06%) had diabetes. DM patients were elderly (mean age of 69.23 years) and the mortality rate was higher (64.38% vs. 52.05%,  $p = 0.036$ ) than in non-DM patients. By multivariate analysis, septic shock was associated with increased mortality in DM patients. Hypoglycemia was associated with increased mortality in non-DM patients only (100% vs. 50.33%,  $p = 0.006$ ). The lowest mortality was for the blood glucose range 70–100 mg/dL in non-DM patients (43.24%) and 100–140 mg/dL for DM patients (56.52%). Increased glycemic variability (coefficient of variation (CV) > 40% compared to < 20%) was associated with increased mortality in non-DM patients (86.36% vs. 47.12%,  $p = 0.003$ ).

*Conclusion:* Effects of dysglycemia on mortality due to CRAB complex bacteremia differ according to diabetic status. Mortality was higher in DM patients. In non-DM patients,

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hypoglycemia and increased CV were associated with increased mortality. The lowest mortality was for the blood glucose range 70–100 mg/dL in non-DM patients and 100–140 mg/dL for DM patients.

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## Introduction

Community acquired Gram-negative bacillus bacteremia is a leading cause of hospitalization, sepsis and mortality.<sup>1</sup> *Acinetobacter baumannii* (AB) complex is an important Gram-negative pathogen that has become an increasingly prevalent cause of bloodstream infections.<sup>2</sup> The *Acinetobacter calcoaceticus-baumannii* complex includes four genospecies: genospecies 1, *A. calcoaceticus*; genospecies 2, *A. baumannii*; genospecies 3, *Acinetobacter pittii*; and genospecies 13TU, *Acinetobacter nosocomialis*. Among these, *A. baumannii* is the most important in the clinical context.<sup>3,4</sup> Multidrug resistance has been identified as an independent risk factor for mortality in patients with AB complex bacteremia.<sup>5</sup>

Diabetes mellitus (DM) and *Acinetobacter* spp. infection are significantly associated with a poor prognosis in critically ill patients with bacteremia.<sup>6</sup> The three domains of glycemic control (hyperglycemia, hypoglycemia, and increased glycemic variability) have been found to be independently associated with increased risk of mortality in critically ill patients.<sup>7</sup> However, studies investigating the role of diabetes and dysglycemia to mortality in AB complex bacteremia are rare or none. This study aimed to investigate the risk factors for mortality and the relationship of diabetic status and glycemic indices (hypoglycemia, hyperglycemia and glycemic variability) to mortality in patients with CRAB complex bacteremia.

## Methods

### Study population and data collection

MacKay Memorial Hospital is a 2200-bed medical center in Northern Taiwan. This retrospective, observational cohort study was conducted by review of medical records of all adult patients aged  $\geq 18$  years hospitalized for CRAB complex bacteremia between the first of January 2010 and 31st December 2015. Only the first bacteremia episode from each patient was included for analysis. This study was approved by the institutional review board of our hospital (14MMHIS052).

Medical records were reviewed for demographic characteristics, comorbid conditions, complications, antibiotics used, laboratory examinations and microbiologic tests. Comorbidity included liver cirrhosis, renal disease, malignancy, stroke, heart disease, chronic obstructive pulmonary disease and immunosuppressive status. Chronic kidney disease was defined as a glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup>. End-stage renal disease was defined as a

GFR  $< 15$  mL/min/1.73 m<sup>2</sup> or receipt of permanent renal replacement therapy for more than 3 months. Immunosuppression was defined as one or more of the following: solid organ or stem cell transplantation, human immunodeficiency virus infection or receipt of corticosteroids at a dosage equivalent to or higher than 15 mg of prednisolone daily for more than 5 days or cytotoxic chemotherapy or other immunosuppressive agents within 4 weeks prior to the first onset of *A. baumannii* bacteremia.

The onset of bacteremia was defined as the day when the blood culture that eventually yielded CRAB complex was obtained. Blood glucose values included first random blood glucose and first fasting plasma glucose values at time of admission, and random and fasting plasma glucose values within 24 h of bacteremia obtained by central laboratory from venous and arterial blood samples. In diabetes patients, glucometer blood glucose values within 24 h of onset of bacteremia were recorded. Hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography method. Minimum blood glucose was the lowest blood glucose value recorded at admission or within 24 h of bacteremia. Criteria for the diagnosis of diabetes was as defined by the American Diabetes Association.<sup>8</sup> Hypoglycemia was defined as blood glucose  $< 70$  mg/dL.<sup>8</sup> Attributable mortality indicated that a patient died during the period of the CRAB complex bacteremia episode.

### Antimicrobial susceptibility testing

Carbapenem-resistant AB complex was defined as resistance to piperacillin, piperacillin-tazobactam, ampicillin/sulbactam, imipenem, ceftazidime, gentamicin, amikacin, tetracycline, chloramphenicol, ciprofloxacin, and cotrimoxazole. Resistance to imipenem was defined as MIC  $\geq 8$  mg/L according to Clinical and Laboratory Standards Institute guidelines.<sup>9</sup> Appropriate antimicrobial therapy was defined as administration of  $\geq 1$  antimicrobial agent, to which CRAB complex was susceptible *in vitro*, within 48 h after the onset of bacteremia, with an approved route and dosage appropriate for end organ function.

### Statistical analysis

All data were analyzed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). Parametric quantitative variables were expressed as mean values  $\pm$  standard deviations and nonparametric quantitative variables as median and interquartile ranges (IQRs). Categorical variables were expressed as percentages of total number of specific patients analyzed. Continuous variables were compared by the Student *t*-test. A Mann–Whitney *U* test was used to analyze

continuous nonparametric data. Categorical data were analyzed by chi-square test with Yates' continuity correction or Fisher's exact test as appropriate. Independent predictors for mortality were identified by logistic regression analysis. Variables with a  $p$  value less  $<0.05$  by the univariate analysis underwent multiple conditional logistic regression analysis.  $P$  value  $< 0.05$  was considered statistically significant.

## Results

From January 1st 2010 to December 31st 2015, a total of 428 adult patients were hospitalized for CRAB complex bacteremia; and data from 317 patients were available for analysis. The demographic and clinical characteristics of DM and nondiabetes (non-DM) patients with CRAB complex bacteremia are shown in Table 1. The mean age was  $66.1 \pm 16.87$  years, mortality rate was 57.73% and 46.06%

(146/317) had diabetes. Compared to those without diabetes, DM patients were elderly (mean age of  $69.23 \pm 12.88$  years) and the mean APACHE II score ( $29.83 \pm 7.82$  vs.  $27.1 \pm 8.65$ ,  $p = 0.006$ ) and mortality rate were higher than in non-DM patients (64.38% vs. 52.05%,  $p = 0.036$ ). More diabetes patients had chronic kidney disease, heart disease, and septic shock than non-DM patients.

Antibiotic susceptibilities of antibiotics used during the study period for carbapenem resistant AB complex were 99.96% for colistin, 44.05% for tigecycline, 6.52% for sulfamethoxazole, 3.90% for gentamicin, 1.92% for ceftazidime and 1.34% for ciprofloxacin. Univariate and multivariate analyses of risk factors for mortality among diabetes patients with CRAB complex bacteremia are shown in Table 2. By multivariate analysis, septic shock was associated with increased mortality.

Fig. 1 and Table 3 show the relation of minimum blood glucose during hospital stay to mortality in 124 DM and 163

**Table 1** Demographic and clinical characteristics of patients with carbapenem-resistant *Acinetobacter baumannii* complex bacteremia.

Characteristics n (%) (mean $\pm$ SD or median, IQR)	Total n = 317	DM n = 146	non-DM n = 171	$p$ value
	Mean $\pm$ SD (n (%)) or interquartile range			
Age, years	66.1 $\pm$ 16.87	69.23 $\pm$ 12.88	63.4 $\pm$ 19.28	0.002
Male sex, n (%)	202 (63.72%)	86 (58.90%)	116 (67.84%)	0.126
Mortality	183 (57.73%)	94 (64.38%)	89 (52.05%)	0.036
Length of hospital stay (d)	36 (18–67.5)	34.5 (18–63.3)	38 (18–72)	0.324
ICU stay, n (%)	280 (88.33%)	127 (86.99%)	153 (89.47%)	0.609
Length of ICU stay (d)	19 (10–34)	21 (10–35)	17.5 (10–34)	0.860
APACHE II score	28.32 $\pm$ 8.38	29.83 $\pm$ 7.82	27.1 $\pm$ 8.65	0.006
Comorbidities, n (%)				
Liver cirrhosis	42 (13.25%)	18 (12.33%)	24 (14.04%)	0.779
CKD/ESRD	108 (34.07%)	61 (41.78%)	47 (27.49%)	0.011
Malignancy	87 (27.44%)	34 (23.29%)	53 (30.99%)	0.160
Stroke	67 (21.14%)	36 (24.66%)	31 (18.13%)	0.200
CAD/CHF	93 (29.34%)	57 (39.04%)	36 (21.05%)	0.001
COPD	45 (14.20%)	19 (13.01%)	26 (15.20%)	0.692
Immunosuppression	105 (33.12%)	42 (28.77%)	63 (36.84%)	0.161
Complications, n (%)				
Septic Shock	214 (67.51%)	110 (75.34%)	104 (60.82%)	0.008
Acute respiratory failure	276 (87.07%)	133 (91.10%)	143 (83.63%)	0.071
Acute renal failure	172 (54.26%)	83 (56.85%)	89 (52.05%)	0.458
Sources of bacteremia, n (%)				
Respiratory tract	182 (57.41%)	82 (56.16%)	100 (58.48%)	0.763
Intra-abdominal	3 (0.95%)	0 (0.00%)	3 (1.75%)	0.252
Skin/soft tissue	10 (3.15%)	6 (4.11%)	4 (2.34%)	0.522
Urinary tract	6 (1.89%)	1 (0.68%)	5 (2.92%)	0.223
CVC	22 (6.94%)	11 (7.53%)	11 (6.43%)	0.871
Surgical site	11 (3.47%)	3 (2.05%)	8 (4.68%)	0.335
Primary	83 (26.18%)	43 (29.45%)	40 (23.39%)	0.273
Neutropenia, n (%)	7 (2.21%)	3 (2.05%)	4 (2.34%)	$>0.99$
Thrombocytopenia, n (%)	120 (37.85%)	54 (36.99%)	66 (38.60%)	0.723
Appropriate antibiotic, n (%)	104 (32.81%)	42 (28.77%)	62 (36.26%)	0.195

APACHE II = Acute Physiology and Chronic Health Evaluation II; CAD = coronary artery disease, CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; DM = diabetes mellitus; ESRD = end stage renal disease; ICU = intensive care unit; neutropenia = total neutrophil count  $< 500$  neutrophils/ $\mu$ L; non-DM = nondiabetes; thrombocytopenia = total platelet count  $< 100,000/\mu$ L.

**Table 2** Univariate and multivariate analyses of risk factors for mortality in 146 diabetes patients with carbapenem-resistant *Acinetobacter baumannii* complex bacteremia.

Risk factor	Univariate analysis			Multivariate analysis		
	Odds ratio	(95% CI)	<i>p</i> value	Odds ratio	(95% CI)	<i>p</i> value
Age (years)	1.03	1.00–1.06	0.030	1.04	1.00–1.08	0.067
Liver Cirrhosis	5.13	1.13–23.27	0.034	0.86	0.14–5.25	0.872
Septic shock	191.47	24.55–1493.13	<0.001	204.86	22.70–1848.41	<0.001
Acute renal failure	3.71	1.82–7.55	<0.001	0.93	0.27–3.18	0.905
NG tube placement	2.96	1.05–8.32	0.040	3.94	0.92–16.82	0.064
Thrombocytopenia	3.48	1.55–7.81	0.002	2.13	0.57–7.90	0.259

CI = confidence interval; NG = nasogastric; thrombocytopenia = platelet count <100,000/ $\mu$ L.

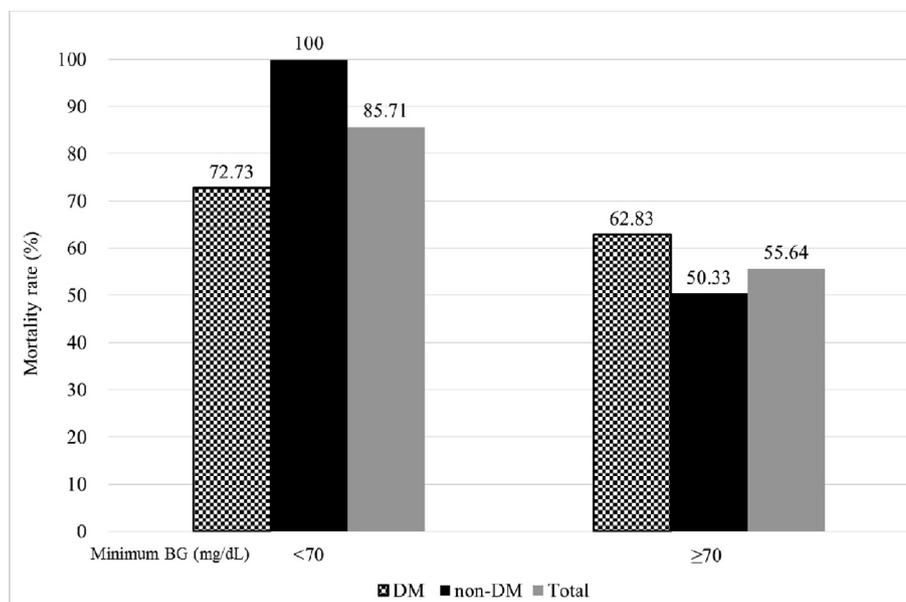
non-DM patients with available central laboratory blood glucose data. In patients without diabetes, there was a twofold increase in mortality in the group with hypoglycemia compared to those with blood glucose  $\geq 70$  mg/dL (100% vs. 50.33%,  $p = 0.006$ ). Although mortality was increased in diabetes patients with hypoglycemia, there was no significant difference compared to those without hypoglycemia ( $p = 0.747$ ).

Fig. 2 and Table 4 show the relation of blood glucose ranges during bacteremia and mortality in 146 DM and 171 non-DM patients with available central laboratory blood glucose values. Blood glucose in the hypoglycemia range was associated with highest mortality in both DM and non-DM patients (80.00% and 85.71% respectively). In DM patients, mortality was least in the blood glucose range 100–140 mg/dL (56.52%), and was higher (63.24–66.67%) in the blood glucose ranges 70–100, 140–180 and  $>180$  mg/dL. Among the non-DM group, the lowest mortality was for the blood glucose range 70–100 mg/dL (43.24%), with increased mortality for blood glucose ranges 100–140 (50.67%) and 140–180 mg/dL (50.0%), and increased further (62.5%) when blood glucose was  $>180$  mg/dL.

Fig. 3 and Table 5 show the relationship between coefficient of variation (CV) and mortality in 124 DM patients and 163 non-DM patients with available central lab blood glucose values at admission and within 24 h of bacteremia. Among non-DM patients, increasing CV was associated with increase in mortality, with an almost twofold increase in mortality (86.36% vs. 47.12%) for those with CV  $\geq 40\%$  compared to CV  $< 20\%$  ( $p = 0.003$ ). However, this relationship was not present in DM patients. The relation between CV and mortality in 93 DM patients with available glucometer blood glucose readings obtained within 24 h of bacteremia is shown in Fig. 4. Increasing CV was not significantly associated with increased mortality ( $p = 0.055$ ).

## Discussion

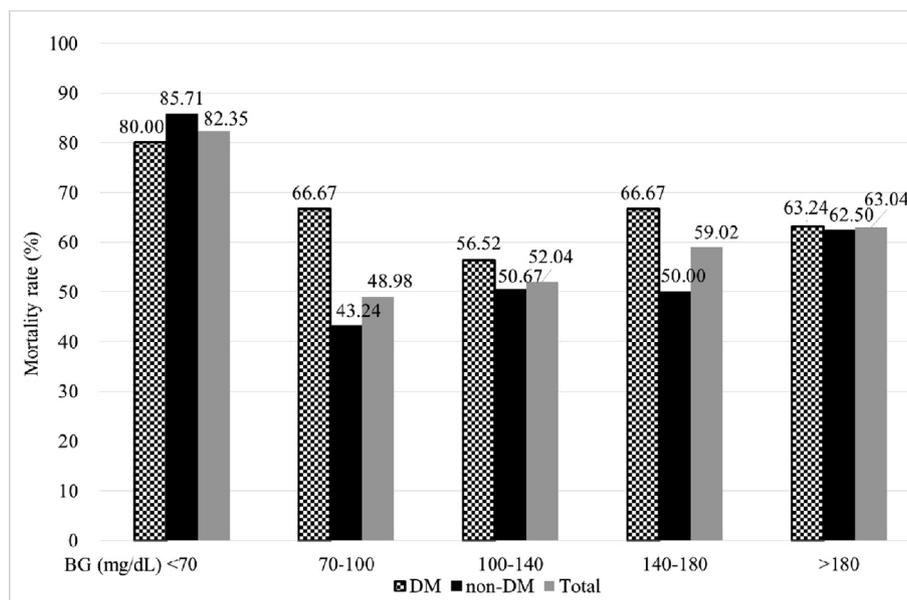
Our study investigated the relation of the domains of glycaemic control to mortality in DM and non-DM patients with CRAB complex bacteremia. We compared our results with those of other studies which focused on dysglycemia in patients who were critically ill or had sepsis.



**Figure 1.** Relation between minimum blood glucose (BG) and mortality in 124 diabetes (DM) patients ( $p = 0.747$ ) and 163 nondiabetes (non-DM) patients ( $p = 0.006$ ) with available central laboratory blood glucose data.

**Table 3** Relation between minimum blood glucose and mortality in 124 diabetes patients ( $p = 0.747$ ) and 163 nondiabetes patients ( $p = 0.006$ ) with available central laboratory blood glucose data.

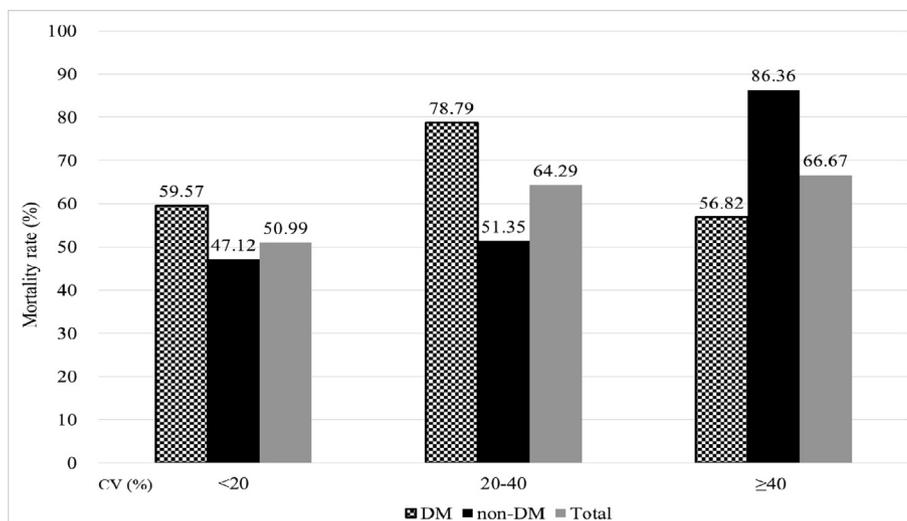
Minimum blood glucose (mg/dL)	Diabetes			Nondiabetes		
	Mortality rate	Mortality no.	Total no.	Mortality rate	Mortality no.	Total no.
<70	72.73%	8	11	100.00%	10	10
≥70	62.83%	71	113	50.33%	77	153

**Figure 2.** Relation of blood glucose ranges during bacteremia and mortality in 146 diabetes (DM) and 171 nondiabetes (non-DM) patients with available central laboratory blood glucose (BG) values.**Table 4** Relation of blood glucose ranges during bacteremia and mortality in 146 diabetes patients and 171 nondiabetes patients with available central laboratory blood glucose values during bacteremia.

Blood glucose range (mg/dL)	Diabetes			Nondiabetes		
	Mortality rate	Mortality no.	Total no.	Mortality rate	Mortality no.	Total no.
<70	80.00%	8	10	85.71%	6	7
70–100	66.67%	8	12	43.24%	16	37
100–140	56.52%	13	23	50.67%	38	75
140–180	66.67%	22	33	50.00%	14	28
>180	63.24%	43	68	62.50%	15	24

In CRAB complex bacteremia, hypoglycemia was associated with significantly increased mortality only in non-DM patients. However, when the relation of blood glucose ranges during bacteremia to mortality was compared, mortality rate was highest in patients with hypoglycemia for both DM and non-DM patients. This is in contrast to data from other observational cohort studies on the critically ill which found that hypoglycemia (defined at different threshold levels, ranging from <70 to < 81 mg/dL) was independently associated with increased risk of mortality in both DM and non-DM populations.<sup>10,11</sup> Krinsky et al. found that hypoglycemia was independently associated with increased mortality in critically ill patients both with and

without diabetes, although the relation was stronger among patients without diabetes.<sup>7</sup> Mild hypoglycemia (blood glucose < 70 mg/dL) has also been found to be independently associated with increased risk of mortality in patients with sepsis.<sup>12</sup> The elderly, chronic kidney disease, severe sepsis and critical illness are risk factors for hypoglycemia, while insulin treatment is an important cause of hypoglycemia. In the landmark Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, among intensive care unit (ICU) patients, mortality was higher in the intensive than in the conventional insulin therapy group.<sup>13</sup> Our data suggest that although hypoglycemia is significantly associated with



**Figure 3.** Relationship between coefficient of variation and mortality in 124 diabetes (DM) and 163 nondiabetes (non-DM) patients with available central lab blood glucose values at admission and within 24 h of bacteremia.

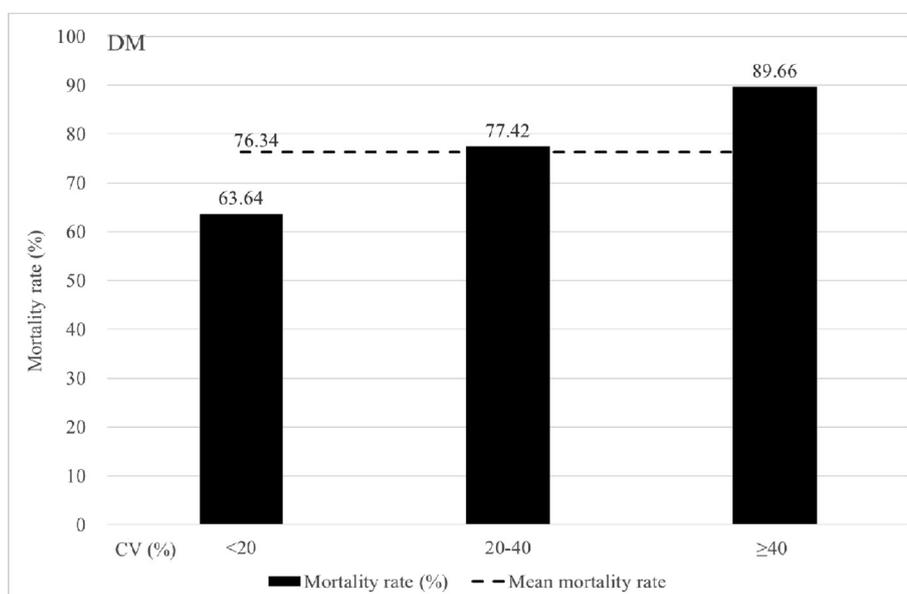
**Table 5** Relationship between coefficient of variation (CV) and mortality in 124 diabetes and 163 nondiabetes patients with available central lab blood glucose values at admission and within 24 h of bacteremia.

CV (%)	Diabetes			Nondiabetes		
	Mortality rate	Mortality no.	Total no.	Mortality rate	Mortality no.	Total no.
<20	59.57%	28	47	47.12%	49	104
20–40	78.79%	26	33	51.35%	19	37
≥40	56.82%	25	44	86.36%	19	22

increased mortality only in non diabetes patients, it is of importance in both DM and non-DM patients.

In non-DM patients, mortality was lowest for the blood glucose range 70–100 mg/dL, and highest when blood

glucose was >180 mg/dL. However, in DM patients, the lowest mortality was for the blood glucose range 100–140 mg/dL, while other blood glucose ranges had similar mortality. Hyperglycemia in hospitalized patients is



**Figure 4.** Relation between coefficient of variation and mortality in 93 diabetes patients with available glucometer blood glucose values within 24 h of bacteremia.

defined as blood glucose levels  $>140$  mg/dL.<sup>8</sup> In patients with sepsis, hyperglycemia is common and related to disease severity.<sup>14</sup> Many studies reported an association between high glucose levels during hospital or ICU stay and mortality in critically ill<sup>15,16</sup> and sepsis patients.<sup>17,18</sup> The majority of patients with bacteremia were critically ill (ICU stay in 88.33%), and our findings are similar to other studies which demonstrated that the association between hyperglycemia and increased risk of mortality was much stronger among nondiabetic individuals than among diabetic individuals.<sup>15,16,19,20</sup> In an international multicenter study on critically ill patients, mortality was lowest when mean blood glucose was 80–110 and 110–140 mg/dL, and increased at higher levels in non-DM patients. Among diabetes patients, mean BG of 80–110 mg/dL was associated with higher mortality risk than blood glucose in other ranges (110–140, 140–180, and  $\geq 180$  mg/dL).<sup>7</sup> Egi et al. demonstrated that ICU mortality increased significantly with increasing mean blood glucose concentration, and hyperglycemia was strongly and independently associated with increased mortality in non-DM patients but not in DM patients.<sup>15</sup> In contrast; severe admission hyperglycemia (blood glucose  $\geq 200$  mg/dL) in critically ill sepsis patients was shown to be associated with increased 30-day mortality, irrespective of the presence or absence of diabetes.<sup>21</sup> Elevated blood glucose levels may be beneficial to the critically ill individual, and stress hyperglycemia is an appropriate and adaptive response to life-threatening illness.<sup>22</sup> The “diabetes paradox” suggests that although diabetes is associated with a large burden of illness in outpatients; diabetes as a comorbidity is not independently associated with increased risk of mortality in patients admitted to intensive care units.<sup>23</sup> Our findings suggest that in both DM and non-DM patients, euglycemia was associated with the lowest mortality in CRAB complex bacteremia.

Increased glycemic variability was independently associated with decreased risk of mortality only in non-DM patients with CRAB complex bacteremia. Glycemic variability has been defined as acute glycemic fluctuations; with both upwards fluctuations (in hypoglycemic correction) and downward fluctuations (in initial overbearing hypoglycemic treatment).<sup>24</sup> Although there are different ways of measuring glycemic variability, there is no consensus on which methods are best at present. Some studies showed that glycemic variability is an independent predictor of mortality in critically ill patients.<sup>25,26</sup> In the Leuven interventional trials, increasing glycemic variability in critically ill patients was associated with increased risk of mortality regardless of diabetic status.<sup>27</sup> However, our findings were similar to other trials which found that low glycemic variability was independently associated with lower risk of mortality and high glycemic variability was independently associated with increased risk of mortality among non-DM individuals but not among diabetic individuals.<sup>16,28</sup> Krinsley et al. demonstrated that increased glycemic variability, defined as  $CV \geq 20\%$ , was independently associated with increased risk of mortality only among patients without diabetes, with a more than a threefold higher mortality among the cohort with  $CV \geq 40\%$  compared with those with  $CV < 20\%$ .<sup>7</sup> It is not known whether glycemic variability is a cause of poor patient outcomes or is a marker of severe illness.<sup>29</sup> A degree of tolerance to glycemic

variability may occur in diabetic patients due to their glycaemic history preceding critical illness.<sup>30</sup>

Diabetes was present in 46.06% of patients with CRAB complex bacteremia. In other studies, 24–31.3% of patients with AB complex bacteremia had diabetes.<sup>6,31</sup> The high prevalence of diabetes reflects the progressive increase of diabetes worldwide. According to the World Health Organization (WHO), the number of people with diabetes worldwide has risen from 108 million in 1980 to 422 million in 2014, while the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.<sup>32</sup> Mortality rates for AB complex bacteremia were 69.9–73% in other studies.<sup>6,33</sup> Mortality was higher among DM patients compared to non-DM patients with CRAB complex bacteremia. This is in contrast to a meta-analysis of 10 studies between 2000 and 2016 which showed that the mortality rate of septic patients with diabetes was slightly lower than that of non-DM patients.<sup>34</sup> The lack of severity adjustment is a significant limitation of the available literature relating to mortality risk of critically ill patients with and without diabetes.<sup>23</sup> Nevertheless, the risk for death among people with diabetes is about twice that of non-DM people of similar age.<sup>35</sup> Diabetes has been projected by the WHO to be the seventh leading cause of death in 2030.<sup>32</sup> Increased mortality in diabetes with CRAB complex bacteremia could be due to other factors. Compared to those without diabetes, DM patients were elderly and had a higher APACHE II score; and septic shock was a risk factor for increased mortality. Our data are concordant to other studies which found older age, higher APACHE II score and septic shock to be risk factors for increased mortality in CRAB complex bacteremia.<sup>36</sup> The status of premorbid glycaemic control could affect sepsis outcome in diabetes patients. In an analysis of critically ill patients with diabetes, higher ( $>7\%$ ) preadmission levels of HbA1c was associated with lower hospital mortality compared with the lower ( $<7\%$ ) HbA1c cohort.<sup>37</sup> Our findings are consistent with Krinsley et al. who noted that critically ill patients with diabetes may benefit from higher glucose target ranges than those without diabetes.<sup>7</sup>

In order to reduce mortality from dysglycemia in critically ill patients, glycemic targets should adequately control blood glucose while avoiding hypoglycemia and hyperglycemia and minimizing glycemic variability. In non-DM patients, tight blood glucose control with a target blood glucose range 70–110 mg/dL could increase the risk of hypoglycemia. The American Diabetes Association recommends that insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold  $\geq 180$  mg/dL.<sup>8</sup> Once insulin therapy is started, a target glucose range of 140–180 mg/dL is recommended for the majority of critically ill and noncritically ill patients.<sup>38</sup> Based on our study results, a target blood glucose goal between 100 and 140 mg/dL could help reduce mortality from CRAB complex bacteremia for DM patients. Diabetes is often asymptomatic and diagnosis delayed. Measurement of fasting blood glucose, post prandial blood glucose and HbA1c in hospitalized patients could help detect previously undiagnosed diabetes as well as provide information on glycaemic control. Optimal glycemic targets and insulin infusion protocols should consider the patient’s diabetic

status, pre-morbid blood glucose control in DM patients, presence of other comorbidity and risk factors for hypoglycemia. Limitations in our study were that it was retrospective, conducted in a single center and HbA1c data was not available for all patients. Many patients were excluded due to lack of data on fasting blood glucose and blood glucose levels during bacteremia.

In summary, our study highlights the role of dysglycemia in mortality due to CRAB complex bacteremia. Effects of dysglycemia on mortality due to CRAB complex bacteremia differ according to diabetic status. Mortality was higher in DM patients; while in non-DM patients, hypoglycemia and increased CV were associated with increased mortality. The lowest mortality was for the blood glucose range 100–140 mg/dL for DM patients with CRAB complex bacteremia. Thus we suggest that maintaining a blood glucose range of 100–140 mg/dL while avoiding hypoglycemia could help reduce mortality in DM patients with CRAB complex bacteremia. Future prospective studies focusing on the relation of the different domains of blood glucose control to mortality according to diabetes status could help identify strategies to reduce mortality from CRAB complex bacteremia.

## Conflicts of interest

The authors declare that they have no conflicting interests.

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## References

- Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997;24:584–602.
- Smolyakov R, Borer A, Reisenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* blood stream infection: risk factors and outcome with ampicillin-sulbactam treatment. *J Hosp Infect* 2003;54:32–8.
- Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin Microbiol Rev* 2008;21:538–82.
- Retailiau HF, Hightower AW, Dixon RE, Allen JR. *Acinetobacter calcoaceticus*: a nosocomial pathogen with an unusual seasonal pattern. *J Infect Dis* 1979;139:371–5.
- Guo N. Risk factors and outcomes of hospitalized patients with blood infections caused by multidrug-resistant *Acinetobacter baumannii* complex in a hospital of Northern China. *Am J Infect Contr* 2016;44:e37–9.
- Leão ACQ, Menezes PR, Oliveira MS, Levin AS. *Acinetobacter* spp. are associated with a higher mortality in intensive care patients with bacteremia: a survival analysis. *BMC Infect Dis* 2016;16:386.
- Krinsley James S, Egi Moritoki, Kiss Alex, Devendra Amin N, Schuetz Philipp, Maurer Paula M, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013;17:R37.
- American Diabetes Association. Standards of medical care in diabetes-2017. *Diabetes Care* 2017;40(Suppl. 1):S11–127.
- Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: twenty-fifth informational supplement CLSI*. Wayne, PA, USA: CLSI document; 2015. M100–S25.
- Krinsley JS, Schultz MJ, Spronk PE, Harmsen RE, van Braam Houckgeest F, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care* 2011;15:R173.
- Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. Hypoglycemia and Outcome in critically ill patients. *Mayo Clin Proc* 2010;85:217–24.
- Park S, Kim DG, Suh GY, Jun Goo Kang JG, Ju YS, Lee YJ, et al. Mild hypoglycemia is independently associated with increased risk of mortality in patients with sepsis: a 3-year retrospective observational study. *Crit Care* 2012;16:R189.
- Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–97.
- Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive Care Med* 2004;30:748–56.
- Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med* 2008;36:2249–55.
- Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009;37:3001–9.
- Stegenga ME, Vincent JL, Vail GM, Xie J, Haney DJ, Williams MD, et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010;38:539–45.
- Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003;78:1471–8.
- Krinsley JS. Glycemic control, diabetic status and mortality in a heterogeneous population of critically ill patients before and during the era of tight glycemic control. *Semin Thorac Cardiovasc Surg* 2006;18:317–25.
- Rady MY, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc* 2005;80:1558–67.
- van Vught LA, Wiewel MA, Klein Klouwenberg PM, Hoogendijk AJ, Scicluna BP, Ong DS, et al. Molecular diagnosis and risk stratification of sepsis consortium. Admission hyperglycemia in critically ill sepsis patients: association with outcome and host response. *Crit Care Med* 2016;44:1338–46.
- Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care Med* 2013;41:e93–4.
- Krinsley JS, Fisher M. The diabetes paradox: diabetes is not independently associated with mortality in critically ill patients. *Hosp Pract* 1995;2012(40):31–5.
- Silva-Perez LJ, Benitez-Lopez MA, Varon J, Surani S. Management of critically ill patients with diabetes. *World J Diabetes* 2017;8:89–96.
- Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med* 2010;38:838–42.
- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008;36:3008–13.
- Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Bergh G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med* 2010;38:1021–9.

28. Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. *J Diabetes Sci Technol* 2009;**3**:1292–301.
29. Clain J, Ramar K, Surani SR. Glucose control in critical care. *World J Diabetes* 2015;**6**:1082–91.
30. Krinsley JS, Meyfroidt G, van den Berghe G, Egi M, Bellomo R. The impact of pre-morbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. *Curr Opin Clin Nutr Metab Care* 2012;**15**:151–60.
31. Huang L, Chen TL, Lee YT, Lee MH, Kuo SC, Yu KW, et al. Risk factors for imipenem-nonsusceptible *Acinetobacter nosocomialis* bloodstream infection. *J Microbiol Immunol Infect* 2014;**47**:311–7.
32. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;**11**:e442.
33. Lee HY, Chen CL, Wu SR, Huang CW, Chiu CH. Risk factors and outcome analysis of *acinetobacter baumannii* complex bacteremia in critical patients. *Crit Care Med* 2014;**42**:1081–8.
34. Wang Z, Ren J, Wang G, Liu Q, Guo K, Li J. Association between diabetes mellitus and outcomes of patients with sepsis: a meta-analysis. *Med Sci Monit* 2017;**23**:3546–55.
35. Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. 2011. Available at: <http://www.govhwd.org/documents/nationaldiabetesfactsheet2011cdfs.pdf>. [Accessed 26 January 2018].
36. Oliveira MS, Prado GVB, Costa SF, Grinbaum RS, Levin AS. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant *Acinetobacter* spp. *J Antimicrob Chemother* 2008;**61**:1369–75.
37. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011;**39**:105–11.
38. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American association of clinical endocrinologists and american diabetes association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;**32**:1119–31.