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ORIGINAL ARTICLE

Prognostic impact of hyperglycemia at onset of methicillin-sensitive *Staphylococcus aureus* bacteraemia

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Abstract Previous reports have associated hyperglycemia to poor outcome among aged and comorbid *Staphylococcus aureus* bacteraemia (SAB) patients. However, the prognostic impact of hyperglycemia in SAB irrespective of age and underlying conditions including a diagnosis of diabetes has received little attention. The objective here was to evaluate the prognostic relevance of hyperglycemia at onset of methicillin-sensitive SAB (MS-SAB). It was a retrospective study of MS-SAB patients. Blood glucose was measured within 24 h of positive blood cultures. The patient cohort was analyzed *en bloc* and by categorization according to age, underlying conditions and a diagnosis of diabetes. Altogether 161 patients were identified. High initial blood glucose levels were observed among diabetics ($p < 0.001$), patients with deep infections ($p < 0.05$) and poor outcome at 28- or 90-days ($p < 0.05$). Receiver operating characteristics presented the glucose cut-off level of 7.2 mmol/L as a significant predictor of mortality with an area under the curve of 0.63 (95% CI 0.52–0.75, $p < 0.05$). Blood glucose ≥7.2 mmol/L connected to higher 28- (9 vs. 20%, $p < 0.05$) and 90-day (14 vs. 29%, $p < 0.01$) mortality. In Cox proportional hazard regression the blood glucose cut-off value of 7.2 mmol/L significantly predicted 90-day mortality (HR, 2.12; 95% CI, 1.01–4.46; $p < 0.05$). Among young and healthy non-diabetics the negative prognostic impact of high glucose was further accentuated (HR 7.46, $p < 0.05$). High glucose levels had no prognostic impact among diabetics. Hyperglycemia at SAB onset may associate to poor outcome. The negative prognostic impact is accentuated among young and healthy non-diabetics.

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Introduction

Staphylococcus aureus is one of the leading bloodstream pathogens and a major cause of both community- and healthcare-associated bacteraemias (SAB) [1, 2]. Parameters such as severe sepsis [3], deep infection foci, e.g. endocarditis [4, 5] and methicillin-resistance [4, 6], may impair prognosis whereas infectious disease specialist consultation [4, 7, 8] is known to improve outcome. Previous studies have demonstrated a deep infection focus in up to 70% of SAB patients [5, 7]. However, despite identification of prognostic parameters and introduction of novel antibiotics [9] the mortality rates remain high and range from 12 to 35% in recent reports [4, 10, 11].

Severe infections may induce a hyper-metabolic state and hyperglycemia [12, 13] through mechanisms such as elevated cytokine and cortisol levels [14, 15] and insulin deficiency [16]. Hyperglycemia exerts various harmful effects including a pro-coagulant action [17] and altered polymorphonuclear leukocyte functions which may hamper leucocyte migration, adherence, phagocytosis and intracellular killing [18–20]. A negative prognostic impact of hyperglycemia has been observed in various infectious diseases such as pneumonia in diabetics [21] and non-diabetics [22, 23] as well as bacteraemia among intensive care unit (ICU) patients [13] and more specifically due to *S. aureus* [11, 24, 25], *Pseudomonas aeruginosa* [26] and other gram-negative bacteria [27] and candidemia [28].

Previous evaluations on the prognostic impact of hyperglycemia in SAB have included aged and comorbid patients with considerable 44–54% occurrence of methicillin-resistance

[11, 24, 25]. Blood glucose has been recorded either as mean levels during the first 7 days after SAB onset [24, 25] or on the day of admission or on the closest day before the blood cultures were drawn [11]. Furthermore, the statistical analyses have been performed with breakpoints for blood glucose results determined in advance [11, 24, 25]. However, high age, comorbidity and MRSA are well known risk factors for poor outcome [2, 4, 6, 8]. To the best of our knowledge the relevance of hyperglycemia in MS-SAB patient cohorts irrespective of age and underlying conditions including a diagnosis of diabetes has not been previously evaluated.

The objective of the present study was to evaluate the impact of hyperglycemia, at onset of MS-SAB, on disease progression and prognosis. We applied receiver operating characteristics analysis to identify a statistically significant blood glucose cut-off value for outcome prediction. Lack of methicillin-resistant *S. aureus* (MRSA) enabled us to avoid the impact of differences in empirical antibiotic therapy.

Methods

Study population

This was a retrospective study recruiting all adult patients ($n = 342$) from Helsinki University Central Hospital in Finland with at least one positive blood culture for *S. aureus* during 2000–2002 and 2006–2007. Two time-periods were included to exclude any unknown temporary differences in personnel or treatment practices. Patients and corresponding *S. aureus* isolates were matched by using the unique personal number given to all residents of Finland. Patient data were retrieved from both electronic (2006–2007) and written (2000–2002) hospital archives. Any possible disadvantage with either information storage pattern was accounted for by including both paper and electronic hospital records. Five cases of MRSA bacteraemia were omitted. Patient records were followed for 90 days. Data collection included gender, age, bacteraemia acquisition, underlying diseases, and length and administration route of any antibiotic therapy. Furthermore, infection focus documentation was based on clinical suspicion or verified by radiological, bacteriological, or pathological investigations. Laboratory results and time to defervescence (axillary temperature below 37.5 °C) were recorded. Primary endpoint was mortality at 28 or 90 days. Secondary endpoints were prevalence of deep infection foci, time to defervescence and length of hospitalization.

Definitions

Community- and healthcare-associated SAB have been defined previously [7]. Modified Duke criteria were applied to define endocarditis [29]. Sepsis in connection with hypotension, hypo-perfusion, or organ failure was classified as severe sepsis whereas sepsis with arterial hypotension despite adequate fluid resuscitation was defined as septic shock [30]. McCabes's criteria were used to classify severity of underlying diseases into healthy and nonfatal or ultimately and rapidly fatal [31]. Infectious disease specialist consultations within 7 days of the first positive blood cultures for *S. aureus* were documented and categorized into (1) formal bedside consultation, (2) informal telephone consultation or (3) no consultation [7].

Antibiotic therapy

Semisynthetic penicillin was defined as the standard antibiotic therapy. Cefuroxime, clindamycin or vancomycin was given to patients with contradictions for penicillin. Rifampicin and fluoroquinolone were provided as additional antibiotic therapy. Proper length of antibiotic therapy was defined as intravenous administration for at least 28 days for deep infection focus and at least 14 days in the absence of any deep infection. Antibiotic indications, dosage and administration routes have been provided in detail previously [32, 33].

Blood glucose

Blood glucose was measured in connection with, shortly before or shortly after blood culture collecting time-points such that all glucose samples were measured within 24 h of blood culture collection.

Statistical analysis

Data is presented either as absolute values and percentages or as median and interquartile ranges (IQR, 25th and 75th

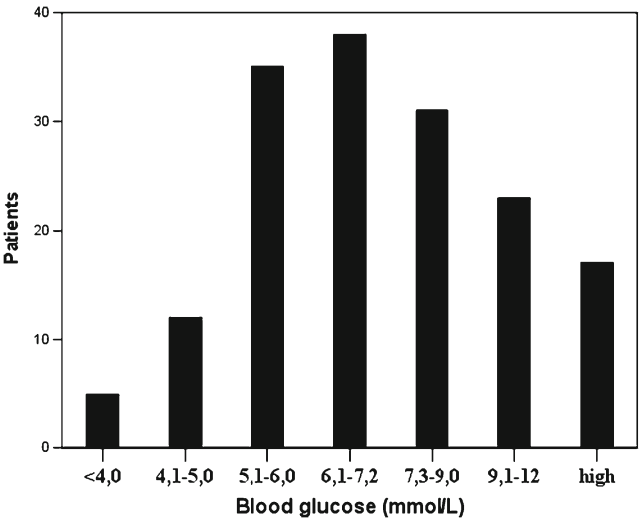

Fig. 1 The distribution of blood glucose concentrations (mmol/L) among 161 patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia within 24 h of blood culture collection

percentiles). Categorical variables are compared with Pearson's $X2$ -test whereas non-parametric data is analyzed with Mann–Whitney *u-test* or Students *t-test*. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Discriminative power of blood glucose in predicting 90-day mortality was evaluated by receiver operating characteristic (ROC) curves. The Youden index was defined as the point on the ROC-curve maximizing both sensitivity and specificity values equally to locate the cut-off point. The ROC-curve derived glucose cut-off point was applied for the Kaplan-Meier estimator method and for Cox proportional hazard regression model predicting mortality. Univariate factors with $p < 0.05$ were allowed for the Cox proportional hazard regression model. All tests were two-tailed and $p < 0.05$ was considered as significant. SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Patient characteristics and blood glucose concentrations

Altogether 342 patients were identified for the study but due to missing blood glucose samples the results of 161 patients are shown. Starting from the day of positive blood cultures each patient was provided with an antibiotic effective in vitro against the *S. aureus* blood isolate. Most patients received a β-lactam antibiotic whereas a minority was provided with

Table 1 Blood glucose concentrations (mmol/L) within 24 h of positive blood culture collection time-point in 161 patients with *Staphylococcus aureus* bacteraemia stratified according to patient demographics, underlying conditions, severity of illness, occurrence of deep infection foci and outcome

Demographics	Total N = 161 *n* (%)	Blood glucose (median + interquartile ranges)		
		Factor present	Factor absent	p-value
Male sex	101 (63)	7.00 (5.90–9.11)	7.20 (5.73–8.70)	NS
Age > 60 years	58 (36)	7.20 (6.18–10.7)	6.70 (5.80–8.50)	NS
Healthcare-associated	68 (42)	7.15 (6.00–8.68)	7.00 (5.80–9.40)	NS
Underlying condition[a]				
Healthy or nonfatal[b]	117 (73)	6.80 (5.85–8.60)	7.35 (6.03–9.45)	NS
Ultimately or rapidly fatal[c]	44 (27)	7.35 (6.03–9.45)	6.80 (5.85–8.60)	NS
Diabetes mellitus	42 (26)	10.4 (6.80–16.8)	6.70 (5.80–7.90)	<0.001
Coronary artery disease	31 (19)	7.20 (6.30–9.30)	6.90 (5.80–8.85)	NS
Acute or chronic liver disease	37 (23)	6.30 (5.60–8.95)	7.15 (5.90–9.08)	NS
Acute or chronic pulmonary disease	22 (14)	7.65 (6.25–9.05)	7.00 (5.80–9.10)	NS
Dialysis (haemo or peritoneal)	12 (7)	7.90 (6.78–9.45)	7.00 (5.85–8.90)	NS
Pre-bacteraemic corticosteroid [c]	9 (6)	7.20 (5.50–8.95)	7.00 (5.90–9.08)	NS
Rheumatic or connective tissue disease	9 (6)	7.10 (5.05–8.20)	7.00 (5.90–9.18)	NS
Non-haematological malignancy	11 (7)	7.20 (5.70–10.1)	7.00 (5.90–8.85)	NS
Hematologic malignancy	19 (12)	8.50 (6.70–9.50)	6.95 (5.80–8.70)	NS
Severity of illness				
Severe sepsis[d]	29 (18)	7.40 (4.80–8.90)	7.00 (5.90–9.08)	NS
Intensive care unit[d]	56 (35)	7.50 (5.65–8.78)	6.90 (5.90–9.10)	NS
Any deep infection	118 (73)	7.20 (5.90–9.30)	6.30 (5.70–7.40)	<0.05
Endocarditis	23 (14)	7.40 (5.80–8.80)	7.00 (5.90–9.10)	NS
Outcome				
Defervescence[e]	93 (58)	7.00 (5.90–9.15)	7.25 (5.80–9.18)	NS
Mortality at 28 days	24 (15)	8.50 (7.00–11.8)	6.70 (5.85–8.60)	<0.05
Mortality at 90 days	35 (22)	8.30 (6.40–10.7)	6.70 (5.80–8.65)	<0.05

Values are expressed as N (%), unless otherwise stated, or as median and interquartile ranges (25th and 75th percentiles). p-values calculated with the Mann-Whitney U-test

NS non-significant

[a] Patients may have ≥ 1 underlying condition

[b] Classification according to McCabe and Jackson [31]

[c] Equals prednisolone 10 mg/day for at least 1 month

[d] At blood culture collection time-point

[e] Defervescence within 1 week

vancomycin (2.5%). The majority of patients received formal bedside infectious disease specialist consultation (66%) whereas only 22% had informal telephone consultation.

The mean blood glucose level close to the time point of positive blood culture drawing was 8.35 ± 4.5 (±SD) mmol/L and the median blood glucose was 7.00 mmol/L. The distribution of blood glucose levels among patients is presented in Fig. 1. Patient demographics, bacteraemia acquisition or underlying conditions had no significant impact on blood glucose with the exception of diabetes that associated to significantly higher blood glucose levels ($p < 0.001$) (Table 1). Severity of illness according to the parameters of severe sepsis and ICU treatment did not influence the blood glucose level. A deep infection focus was diagnosed in 73% of patients and it was associated to significantly higher blood glucose levels ($p < 0.05$), although this trend was not observed for endocarditis (Table 1).

Outcome, defervescence and hospitalization

No significant association between blood glucose and time to defervescence was observed (Table 1). The total case fatality in 161 patients at 28 days was 15% and at 90 days 22%. Mean blood glucose levels were significantly higher among patients who died within 28 or 90 days (Table 1). The mean (±SD) time of hospitalization for patients that survived was 36 (±32) days.

Cut-off values for glucose in predicting mortality

By ROC-analysis blood glucose at the time-point for positive blood cultures was a significant predictor for mortality. The area under the curve (AUC) in the ROC analysis was 0.63 (95% CI 0.52–0.75, $p < 0.05$) and produced a cut-off value of 7.2 mmol/L that predicted 90-day mortality (Fig. 2).

The whole patient cohort was stratified according to the blood glucose cut-off value of 7.2 mmol/L. A diagnosis of diabetes (OR 4.47, $p < 0.001$) was the only demographic parameter associated with blood glucose levels above the cut-off value (Table 2). The blood glucose cut-off level connected significantly to higher 28- (OR 3.01, $p < 0.05$) and 90-day (OR 3.12, $p < 0.01$) mortality. Moreover, patients with blood glucose < 7.2 mmol/L who survived had significantly shorter time of hospitalization as compared to those with blood glucose > 7.2 mmol/L ($p < 0.05$). Kaplan-Meier analysis for the whole patient cohort associated patients with blood glucose levels above the cut-off value of 7.2 mmol to significantly higher mortality (log-rank 0.005) (Fig. 3).

Parameters in univariate analysis with significantly elevated risk for 90-day mortality were severe sepsis (OR 3.35, $p < 0.01$), informal telephone infectious disease specialist consultation (OR 2.65, $p < 0.05$), blood glucose cut-off value of 7.2 mmol/L (OR 3.01, $p < 0.01$) and age > 60 years (OR 2.28, $p < 0.05$). In contrast, lack of severe underlying diseases (McCabe's healthy or nonfatal classification) (OR 0.13, $p < 0.001$), formal bedside infectious disease specialist consultation (OR 0.15, $p < 0.001$) and rifampicin therapy for at least 14 days (OR 0.18, $p < 0.001$) were associated with better prognosis. In the Cox proportional hazard regression model, the independent prognostic parameters were age > 60 years (HR 3.78, $p = 0.001$), McCabe's healthy or nonfatal classification (HR 0.26, $p < 0.001$), severe sepsis (HR 2.83, $p < 0.01$), rifampicin therapy for at least 14 days (HR 0.23, $p = 0.001$), formal bedside infectious disease specialist consultation (HR 0.26, $p = 0.001$) and a blood glucose cut-off value of 7.2 mmol/L (HR 2.12, $p < 0.05$) (Table 3).

Furthermore, the Cox proportional hazard regression model of Table 3 was re-performed with the patient cohort categorized according to age, underlying conditions and a diagnosis of diabetes. When including only previously healthy (McCabe's healthy-nonfatal classification) non-diabetics (mean age 48.5 ± 17.5 years) the blood glucose cut-off value of 7.2 mmol/L associated with poor outcome in Cox proportional hazard regression model (HR 7.46, $p < 0.05$) (Table 4). However, when including only diabetic patients, irrespective of underlying conditions or age, the blood glucose cut-off value of 7.2 mmol/L had no prognostic impact.

Discussion

The main finding of the present study was a poor prognostic impact associated with hyperglycemia at the time of detection of SAB. During the 90-days follow-up patients with hyperglycemia within 24 h of the blood culture collection time-

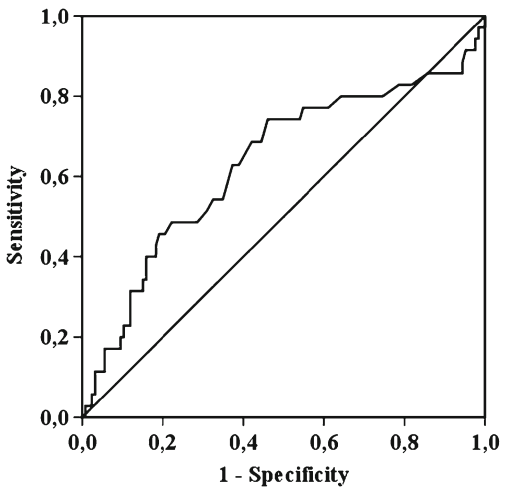

Fig. 2 Receiver operating characteristic (ROC) curve for blood glucose concentration (mmol/L) at blood culture collecting time-point for predicting 90-day mortality in patients with *Staphylococcus aureus* bacteraemia ($n = 161$). The area under the curve (AUC) was 0.63 (95% CI 0.52–0.75) ($p < 0.05$) and the optimal cut-off value 7.2 mmol/L with sensitivity of 69% and specificity of 58%

Table 2 Patient demographics, underlying conditions, severity of illness and outcome in 161 *Staphylococcus aureus* bacteraemia patients stratified according to blood glucose cut-off value 7.20 mmol/L at the time of blood culture collection

Demographics	Glucose < 7.2 mmol/L (*N* = 77)	Glucose > 7.2 mmol/L (*N* = 84)	OR (95% CI)	p-value
Male sex	55 (71)	46 (55)	0.78 (0.41–1.48)	NS
Age > 60 years	26 (34)	32 (38)	1.59 (0.83–3.03)	NS
Healthcare-associated	34 (44)	34 (40)	1.16 (0.62–2.18)	NS
Underlying condition[a]				
Healthy or nonfatal[b]	64 (83)	53 (63)	0.69 (0.34–1.38)	NS
Ultimately or rapidly fatal[b]	20 (26)	24 (29)	1.45 (0.72–2.91)	NS
Diabetes mellitus	11 (14)	31 (37)	4.47 (2.05–9.76)	<0.001
Coronary artery disease	12 (16)	19 (23)	1.97 (0.88–4.38)	NS
Acute or chronic liver disease	22 (29)	15 (18)	0.68 (0.32–1.44)	NS
Acute or chronic pulmonary disease	8 (10)	14 (17)	2.11 (0.83–5.35)	NS
Dialysis (haemo or peritoneal)	4 (5)	8 (10)	2.32 (0.67–8.03)	NS
Pre-bacteraemic corticosteroid[c]	4 (5)	5 (6)	1.39 (0.36–5.37)	NS
Rheumatic or connective tissue disease	5 (6)	4 (5)	0.87 (0.22–3.35)	NS
Non-haematological malignancy	5 (6)	6 (7)	1.34 (0.39–4.57)	NS
Hematologic malignancy	8 (10)	11 (13)	1.58 (0.60–4.17)	NS
Severity of illness				
Severe sepsis[d]	13 (17)	16 (19)	1.43 (0.64–3.21)	NS
Intensive care unit[d]	25 (32)	31 (37)	1.59 (0.83–3.06)	NS
Any deep infection	57 (74)	61 (73)	1.81 (0.88–3.69)	NS
Endocarditis	11 (14)	12 (14)	1.23 (0.51–2.97)	NS
Outcome				
Defervescence[e]	51 (66)	42 (50)	0.76 (0.38–1.52)	NS
Mortality at 28 days	7 (9)	17 (20)	3.01 (1.21–8.00)	<0.05
Mortality at 90 days	11 (14)	24 (29)	3.12 (1.36–6.67)	<0.01
Hospitalization (days) (mean ± SD)[f]	34 (±19)	44 (±27)	–	<0.05

Odds ratio (OR) and 95% confidence intervals (95% CI) are presented. Values are expressed as *n* (%) unless otherwise stated, or mean ± standard deviation (SD)

NS non-significant

[a] Patients may have ≥ 1 underlying condition

[b] Classification according to McCabe and Jackson [31]

[c] Equals prednisolone 10 mg/day for at least 1 month

[d] At blood culture collection time-point

[e] Defervescence within 1 week

[f] Students *t*-test

point had more than a 2-fold higher hazard ratio for a fatal outcome when adjusting for all other prognostic parameters. The negative prognostic impact of hyperglycemia was accentuated when including only young and previously healthy non-diabetics. However, hyperglycemia had no prognostic impact among patients with a diagnosis of diabetes.

Previous studies have identified parameters with indisputable prognostic impact in SAB such as old age and underlying conditions [2, 4, 6], severe sepsis [3] and infectious disease specialist guided therapy management [4, 7, 8]. Many studies report the occurrence of diabetes [2, 4, 5, 8, 24, 25, 33] or other factors that may influence glucose balance, e.g. corticosteroid therapy [2, 5, 8, 33]. However, few studies on SAB report separate laboratory tests, e.g. blood glucose, and to the best of our knowledge only three reports have evaluated the impact of glucose balance on outcome in SAB [11, 24, 25].

The results of the present study with a poor prognostic impact due to hyperglycemia at the initial phase of a severe infection are in line with many previous reports [11, 22–26, 28]. However, previous studies have applied various measurement time-points and different categorization patterns of blood glucose. This makes comparison of results challenging. Some authors report blood glucose levels at hospital admission or at the closest day before blood culture drawing [11, 22, 23] or report an average blood glucose concentration within 48 h of positive blood cultures [26]. In some reports the mean

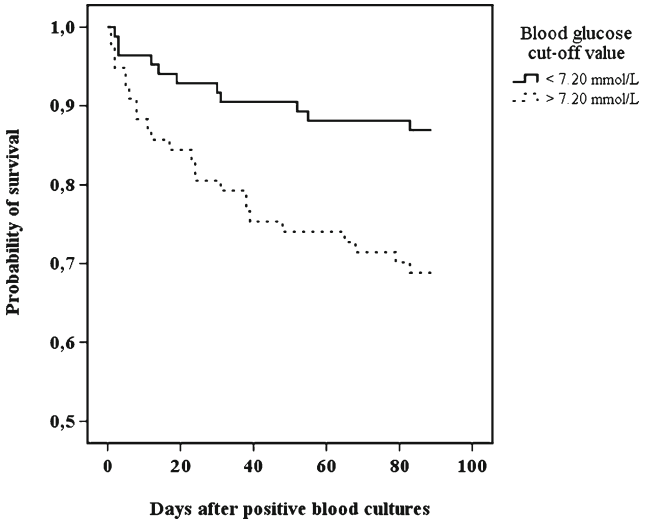

Fig. 3 Kaplan-Meier interpretation for 90-day mortality in patients with *Staphylococcus aureus* bacteraemia ($n = 161$) categorized according to the receiver operating characteristics (ROC) analysis related blood glucose cut-off value of 7.2 mmol/L (log-rank 0.005)

blood glucose levels were derived by averaging highest daily glucose values within the 7 days after infection onset [24, 25, 28] or blood glucose levels from one day prior until 5 days after onset of infection [13]. Most authors stratify results according to blood glucose levels exceeding 167–170 mg/dl (i.e. 9.3–9.4 mmol/L) [11, 24, 25] or the range of 6–13.9 mmol/L [23, 28]. The ROC analysis in the present study presented a glucose cut-off value of 7.2 mmol/L that is lower compared to the breakpoint values applied in previous reports [11, 24, 25, 28]; although one study applied an even lower value of 6.0 mmol/L [23]. To the best of our knowledge, the glucose breakpoint values in earlier reports have been determined a priori whereas one study applied a CART-analysis (classification and regression tree analysis) to define a breakpoint in the average concentration of blood glucose in the first 48 h after positive blood cultures [26]. Thus, as far as we know, the present study is the first to apply ROC analyses to identify a statistically significant blood glucose cut-off value for mortality in severe systemic infections such as SAB.

A recent report observed that hyperglycemia during the first 7 days among SAB patients resulted more often in discharge to a long-term care facility or inpatient rehabilitation [25]. The present study did not record discharge addresses. However, length of hospitalization among patients that survived was analyzed and hyperglycemia at the initial phase of SAB associated with significantly longer hospital stay. Furthermore, previous reports concluded that hyperglycemia may reflect infection severity and outcome in non-diabetic patients but not in diabetic patients [34, 35]. The results of the present study are in line with these two reports as the poor prognostic impact of hyperglycemia in SAB was accentuated among previously healthy non-diabetics whereas among

Table 3 Cox proportional hazard regression model for prognostic factors of 90-day mortality in *Staphylococcus aureus* bacteraemia patients ($n = 161$)

Patient characteristics	Univariate analysis				Cox regression analysis	
	Died $N = 35$ (22%)	Survived $N = 126$ (78%)	OR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	22 (63)	79 (63)	1.01 (0.46–2.19)	NS	–	–
Age > 60 years	18 (51)	40 (32)	2.28 (1.06–4.88)	<0.05	3.78 (1.78–8.05)	0.001
Healthy or nonfatal disease[a]	13 (37)	104 (83)	0.13 (0.06–0.29)	<0.001	0.26 (0.13–0.53)	<0.001
Severity of illness						
Glucose cut-off 7.2 mmol/L[b]	11 (31)	24 (19)	3.01 (1.36–6.67)	<0.01	2.12 (1.01–4.46)	<0.05
Intensive care unit[b]	16 (46)	40 (32)	1.81 (0.84–3.89)	NS	–	–
Severe sepsis[b]	12 (34)	17 (13)	3.35 (1.41–7.95)	<0.01	2.83 (1.39–5.78)	<0.01
Endocarditis	6 (17)	17 (13)	1.33 (0.48–3.67)	NS	–	–
Pneumonia	19 (54)	49 (39)	1.87 (0.88–3.97)	NS	–	–
Additional antibiotic therapy						
Rifampicin therapy ≥ 14 days	8 (23)	78 (62)	0.18 (0.08–0.43)	<0.001	0.23 (0.09–0.54)	0.001
Fluoroquinolone therapy	14 (40)	67 (53)	0.59 (0.27–1.26)	NS	–	–
Infectious specialist consultation						
Bedside formal consultation	11 (31)	95 (75)	0.15 (0.07–0.34)	<0 .001	0.26 (0.12–0.57)	0.001
Telephone informal consultation	13 (37)	23 (18)	2.65 (1.16–6.02)	<0.05	–	–

Hazards ratio (HR) and 95% confidence intervals (95% CI) are presented. Values are expressed as *n* (%), unless otherwise stated

NS non-significant

[a] Classification according to McCabe and Jackson [31]

[b] At positive blood culture collection time-point

Table 4 Cox proportional hazard regression model for prognostic factors of 90-day mortality in *Staphylococcus aureus* bacteraemia patients categorized to include healthy non-diabetics ($n = 91$), Hazards ratio (HR), and 95% confidence intervals (95% CI)

Parameters	Univariate analysis				Cox regression analysis	
	Died $N = 8$ (9%)	Survived $N = 83$ (91%)	OR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	3 (38)	50 (60)	0.39 (0.09–1.77)	NS	–	–
Age > 60 years	2 (25)	21 (25)	0.98 (0.18–5.25)	NS	–	–
Glucose cut-off 7.2 mmol/L[a]	6 (75)	27 (33)	6.22 (1.18–32.9)	<0.05	7.46 (1.48–37.6)	<0.05
Intensive care unit[a]	5 (63)	24 (29)	4.09 (0.91–18.5)	NS	–	–
Severe sepsis[a]	3 (38)	11 (13)	3.93 (0.82–18.8)	NS	–	–
Endocarditis	3 (38)	14 (17)	2.96 (0.63–13.8)	NS	–	–
Pneumonia	6 (75)	32 (39)	4.78 (0.91–25.2)	<0.05	–	–
Rifampicin therapy ≥ 14 days[b]	2 (25)	54 (65)	0.18 (0.03–0.94)	<0.05	–	–
Bedside consultation[c]	2 (25)	68 (82)	0.07 (0.01–0.40)	<0.001	0.07 (0.01–0.36)	<0.01
Telephone consultation[c]	4 (50)	12 (14)	5.92 (1.30–26.9)	<0.05	–	–

Values are expressed as *n* (%), unless otherwise stated

NS non-significant

[a] At positive blood culture collection

[b] Additional antimicrobial therapy

[c] Infectious specialist consultation

diabetics the initial blood glucose levels had no influence on outcome.

To the best of our knowledge, this is the first study evaluating the connection between hyperglycemia determined within 24 h of positive blood cultures and prognosis among SAB patients. The patient cohort was stratified according to ROC analysis derived blood glucose cut-off value and attempts were made to control reasons for differences in outcome between the various groups. Many of the parameters with prognostic impact in the present study have been identified earlier, i.e. age and underlying conditions [2, 4, 6], severe sepsis [3], adjunctive rifampicin therapy [32] and infectious disease specialist consultation [7, 36].

Altogether 73% of patients had deep infection foci. This is in line with the studies presenting deep focus occurrence among 68–74% of SAB patients [5, 7]. Patients with a deep infection focus had significantly higher blood glucose levels, although this difference was not observed for patients with endocarditis nor when categorizing patients according to the ROC analysis related cut-off value of 7.2 mmol/L. Our study is not able to present any explanation for the association between hyperglycemia at the initial phase of SAB and presence of a deep infection focus, and diabetics were not overrepresented among patients with a diagnosed deep infection focus. Previous reports on hyperglycemia and SAB do not comment on any association between blood glucose and infection foci [11, 24, 25].

The present study deviates from previous reports on hyperglycemia and SAB with respect to age and comorbidity [11, 24, 25]. In the present study only one third of patients were aged over 60 years and almost three fourths had a healthy- or nonfatal McCabe's classification regarding underlying conditions. However, in previous reports the mean age has ranged from 68 to 72 years with mean Charlson's comorbidity index of 1.5–4.6 [11, 24, 25]. Thus, the results of the present study apply to a younger and less ill patient cohort as compared to previous reports.

The present study includes limitations that relate to its retrospective nature. First, parameters that may influence blood glucose were only partially documented. The retrospective study design did not enable documentation of any ongoing medications prior to blood culture collection. This is an evident weakness as it is well known that, in addition to diabetes related therapies like insulin, various other medications may cause blood glucose level fluctuations, e.g. non-steroidal anti-inflammatory drugs may alter insulin release from beta cells [37]. In addition, any infusion fluids administered in connection with blood culture collection were undocumented. Hence, as some infusion fluids contain glucose it is possible that the etiology of hyperglycemia during blood culture collection time-point in some patients may have been iatrogenic. Second, we recorded only one glucose measurement within 24 h of blood culture collection. The documentation of several glucose values would have enabled more precise analysis either (1) as an arithmetic mean of several values [26] or (2) as a time-weighted analysis [38]. Third, the blood glucose measurements, within 24 h of blood culture collection, were drawn irrespective of time and fasting, i.e. recent intake of food or

liquids. Fourth, the magnitude of the n-number in the present study (161) is slightly higher than that of two previous reports (100–135) [24, 25], although lower than in a third study (340) [11] on hyperglycemia and SAB. Furthermore, the retrospective nature of the study did not allow for any glycemic control and hence further research is needed to determine whether continuous monitoring and control of elevated glucose levels influence the outcome of SAB.

In conclusion, despite the retrospective study design, low n-number and lack of information regarding background medication and fasting, the present study demonstrated a negative prognostic impact of hyperglycemia in the early phase of SAB. The negative prognostic impact was accentuated among young and healthy non-diabetics. Future prospective studies are needed to establish the relevance of underlying medication, fasting and glycemic control on outcome in SAB.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement The trial was approved by The Institutional Review Board of Helsinki University Central Hospital and The Ethical Committee of Helsinki University Central Hospital. A written informed consent was provided by each patient.

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