Internal and Emergency Medicine (2021) 16:719–728
https://doi.org/10.1007/s11739-020-02507-9

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The association of diabetes and hyperglycemia with sepsis outcomes: a population-based cohort analysis

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Received: 8 February 2020 / Accepted: 12 September 2020 / Published online: 22 September 2020

Abstract

The independent association of diabetes and hyperglycemia on the outcomes of sepsis remains unclear. We conducted retrospective cohort analyses of outcomes among patients with community-onset sepsis admitted to Shamir Medical Center, Israel (08-12/2016). Statistical associations were queried by Cox and logistic regressions, controlled for by matched propensity score analyses. Among 1527 patients with community-onset sepsis, 469 (30.7%) were diabetic. Diabetic patients were significantly older, with advanced complexity of comorbidities, and were more often exposed to healthcare environments. Despite statistically significant univariable associations with in-hospital and 90-day mortality, the adjusted Hazard Ratios (aHR) were 1.21 95% CI 0.8–1.71, $p=0.29$ and 1.13 95% CI 0.86–1.49, $p=0.37$, respectively. However, hyperglycemia at admission (i.e., above 200 mg/dl (was independently associated with: increased in-hospital mortality, aHR 1.48 95% CI 1.02–2.16, $p=0.037$, 30-day mortality, aHR 1.8 95% CI 1.12–2.58, $p=0.001$), and 90-day mortality, aHR 1.68 95% CI 1.24–2.27, $p=0.001$. This association was more robust among diabetic patients than those without diabetes. In this study, diabetes was not associated with worse clinical outcomes in community-onset sepsis. However, high glucose levels at sepsis onset are independently associated with a worse prognosis, particularly among diabetic patients. Future trials should explore whether glycemic control could impact the outcomes and should be part of the management of sepsis, among the general adult septic population.

Keywords Diabetes · Hyperglycemia · Sepsis · Community-acquired infections · Multi-drug resistant · MDR

Introduction

Increasing prevalence of obesity and aging of the population have culminated into an exponential rise in the worldwide rates of diabetes mellitus (DM), imposing a significant burden on individuals and on public health [1]. Sepsis incidence is increasing as a cause of morbidity and mortality in the population [2]. People of advanced age and patients with preexisting chronic health conditions are particularly prone to develop severe sepsis [3].

The association between DM and the risk for infections has been well established [4, 5], although the exact mechanisms are not well understood [6]. The estimated prevalence of DM among adults is 10–20%, but they comprise 20–35% of patients with sepsis [7]. Possible explanations for the higher rates of infections among DM patients are poor chronic glycemic control and/or acute hyperglycemic states, which impairs the immune system, impairs tissue perfusion, and results in gastrointestinal and urinary tract dysmotility,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11739-020-02507-9) contains supplementary material, which is available to authorized users.

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damaged wound healing, and increased healthcare encounters and interventions [8–11]. Comparative controlled analyses of sepsis outcomes among patients with or without DM are conflicting. In some studies, diabetes was associated with increased mortality, a longer length of stay, and higher costs [12, 13]. Other controlled studies, did not find an independent association between DM and increased mortality in sepsis [14], and some even described a protective effect [15]. Inflammatory response of patients with DM during sepsis is altered [16] hence diabetic patients may be less likely to develop adult respiratory distress syndrome (ARDS) [17] and respiratory failure [15]. Diabetic patients have reduced activity of neutrophils and reduced migration of these cells to the lungs with the result of less oxidative damage [17].

The prognostic value of blood glucose levels at admission (ABGL) on sepsis outcomes is also a matter of controversy: in some studies, elevated blood glucose levels at sepsis onset were associated with worse outcomes, [18] yet in others, the association was less established [19–22]. Our study aims were to evaluate the prognostic impact of DM and ABGL on outcomes of sepsis.

Methods

Retrospective analyses were conducted on patients admitted to Shamir (Assaf Harofeh) Medical Center from August to December 2016. The study was approved by the local ethics (Helsinki) committee prior to its initiation.

Consecutive adult patients (> 18 years) with sepsis upon admission (i.e., "community-onset" infection), as per established definition [23], were enrolled. Patients were excluded if they were directly transferred from another facility, or if they were hospitalized in the past 7 days for any reason, or in the past 30 days with the same infectious clinical syndrome. Therefore, "hospital-acquired" infections were excluded, but "community-onset" infections, consisting both of "community-acquired" and of "healthcare-associated" infections, as per established definition [24], were enrolled. The study cohort consisted of patients from whom blood cultures were drawn in the first 2 calendar days of hospitalization (including visits to, and immediate discharge from, the emergency room), who concurrently had systemic inflammatory response syndrome [25]. This screening methodology for diagnosing sepsis had displayed a sensitivity of 100% and a specificity of 99% in a prior pilot analysis [23]. Patients were excluded if they had new-onset DM (diagnosed during the index hospitalization), or if they had gestational DM. ABGL were drawn at the emergency department. For our purposes, elevated BGL were considered > 200 mg/dl, as the accepted definition for stress hyperglycemia [26–29]. Data were extracted from electronic and hard-copy records and included demographics, chronic and background co-morbidities and conditions, various exposures to healthcare, acute illness indices, and outcomes. We also analyzed and quantified multiple parameters associated with diabetes severity (e.g., duration, level of glycemic control, HbA1C, target-organ damages), for stratification purposes. Post-hospitalization mortality data were extracted from a national registry governed by the Israeli Ministry of Interior.

The index pathogen was considered a pathogen isolated from blood (except skin contaminants as determined by the US Centers for Disease Control and Prevention) [30], or from a body site associated with the patient's clinical syndrome: e.g., a pathogen isolated from urine, of a patient with a urinary tract infection. Multi-drug resistant (MDR) phenotype were determined according to an established definition [31], and MDR organisms (MDRO) included: methicillin-resistant *Staphylococcus aureus* (MRSA); ampicillin- and/or vancomycin-resistant *Enterococcus* (VRE); penicillin and/or ceftriaxone non-susceptible *Streptococcus pneumoniae; Acinetobacter baumannii; Pseudomonas aeruginosa*; other inherent carbapenem non-susceptible Gram-negatives (e.g., *Stenotrophomonas maltophilia, Burkholderia cepacia*); and *Enterobacteriaceae* non-susceptible to ≥ 1 of third-generation cephalosporin (e.g., ceftriaxone, ceftazidime, cefotaxime) and/or ≥ 1 carbapenem (CRE), and/or evidence of extended-spectrum beta-lactamase (ESBL) and/or carbapenemase (CPE) production [32].

Statistical analyses

Power calculations predicted that an overall sample size of 1302 subjects (of which 977 non-diabetic patients and 325 diabetic patients) will achieve 90% power at a 0.01 significance level to detect a difference of 10% in survival between non-diabetic and diabetic patients, assuming 70% vs. 80% survival rate at 90 days for patients with vs. without diabetes given that in previous studies diabetic patients comprised 20–35% of patients with sepsis [7] and the mortality rate from sepsis in recent studies was 20–30% at 90 days [33].

All analyses were performed using SPSS software (IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). A two-tailed $p < 0.05$ was considered statistically significant.

Normal distribution was evaluated by histogram and Q–Q plot. Since all continuous data did not distribute normally, they are expressed as a median and interquartile range (IQR). Categorical data are expressed as frequencies and percentages and compared among groups using Chi-square tests and Fisher's exact test. Continuous variables were compared using the Mann–Whitney test. Kaplan Meier's curve and the log-rank test were used to describe mortality during the follow-up period comparing between diabetic and non-diabetic patients.

Multivariable logistic regression was used to study the association between of DM and morbidity outcomes while multivariable Cox regression was used to study the association of DM with survival, both while controlling for possible confounders. The multivariate regression included four blocks: In the first block DM was entered to report the crude association, in the second block, age and gender were added using enter method, in the third block clinical syndrome variables were entered and in the last block, pathogen variables were entered. The variables found to be with a p value higher than 0.1 were removed (using backward method, Wald test).

Propensity score was calculated using logistic regression as the probability of patients to have DM. DM, age, sex, CHF, CKD, dementia, malignancy, Duke's criteria, positive culture, clinical syndrome, and bacterial growth were included in the propensity score calculation. Propensity score was divided into quintiles and then stratified Cox regression and conditional logistic regression were applied.

Results

Descriptive characteristics of the study's cohort

Among 1527 patients with community-onset sepsis, 469 (30.7%) were diabetic. Diabetic patients were significantly older (75 vs. 59 years, $p<0.001$), with advanced complexity of comorbidities (Charlson's combined condition score 7 (5–8) vs. 2 (0–5), $p<0.001$). They were more often exposed to healthcare environments (53.3% among diabetic vs. 36% of non-diabetics had at least one criterion of the Duke-2002 criteria for healthcare-associated infection ($p<0.001$)) and to procedures- 17.6% of diabetics vs. 14.1% of non-diabetics underwent an invasive procedure in the preceding 6 months ($p=0.06$). MDRO infections (15.4% vs. 8.7%; $p<0.001$) and *S. aureus* bloodstream infections (both MRSA and MSSA, 2.3% vs. 0.9%; $p=0.02$), were more common among diabetics as well as skin and soft tissue infection (19.2% vs. 12.2% $p<0.001$). There were no differences in other sepsis features. Baseline characteristics of the study population are depicted in Table 1. Acute illness indices were also more severe among diabetics, including the prevalence of severe sepsis, septic shock, or multi-organ failure (40% vs. 24%; $p<0.001$), need to be admitted directly to an intensive care unit (ICU, 11% vs. 7%; $p=0.01$), acute kidney injury (35% vs. 17%; $p<0.001$), and altered consciousness (35% vs. 20%; $p<0.001$). Also, only 64.4% of patients with DM received appropriate antibiotic therapy within 48 h vs. 77.6% in non-diabetics ($p=0.002$).

Patients with sepsis and hyperglycemia upon admission (both diabetics, $n=183$, and non-diabetics, $n=33$) were older, and had more co-morbidities compared to patients with ABGL < 200 mg/dl (Supplementary Table 1). Diabetic patients with ABGL of > 200 mg/dl were characterized by higher baseline HbA1c levels (7.83% vs. 6.5%, $p<0.001$) and their glucose control regimen included more often insulin (49.2% vs. 28.3%, $p<0.001$). The mean blood glucose during hospitalization was 203 mg/dl among DM with ABGL > 200 mg/dl vs. 146 mg/dl among DM patients with ABGL < 200 mg/dl ($p<0.001$, Supplementary Table 2).

Sepsis outcomes among diabetic vs. nondiabetic patients

The 90 days' survival rate was 78% in the DM group and 88% in the non-DM group ($p<0.001$; Fig. 1). However, despite the significant association of DM with 90-day mortality (HR = 2.0, 95% CI 1.54–2.60; $p<0.001$) (Table 2), this did not remain independently associated as per multivariable analysis (HR = 1.13, $p=0.37$). Among those who survived the index hospitalization, DM was also significantly associated with worse morbidity outcomes: e.g., functional status deterioration (OR 1.95, 95% CI 1.36–2.78; $p<0.001$), and discharge to a long-term care facility (LTCF) after being admitted to the index hospitalization from home (OR 1.77, 95% CI 1.05–3.00; $p=0.032$). However, these associations were also not independent as per multivariable analyses (aOR = 1.13, $p=0.54$, and aOR = 0.87, $p=0.6$, respectively). Stratification of the cohort into PS quintiles revealed no associations between DM and the various outcomes that were queried (Table 2).

Sepsis outcomes stratified by the glucose levels upon admission to the acute-care hospital

Mortality rates were higher for patients with ABGL > 200 mg/dl (Fig. 2): i.e., in-hospital (19.4% vs. 7.6% $p=0.012$, 30 days (19.9% vs. 8.3% $p<0.001$) and 90 days (29.2% vs. 13.3% $p<0.001$). The increment in mortality rates remained significant after multivariable regression analyses, i.e., aOR 1.48 (95% CI 1.02–2.16, $p=0.037$) for in-hospital mortality, 1.8 (95% CI 1.12–2.58, $p=0.001$) for 30-day mortality, and 1.68 (95% CI 1.24–2.27, $p=0.001$) for 90-day mortality (Table 3). Hyperglycemia upon admission was also significantly and independently associated with worse morbidity outcomes (Supplementary Table 1).

In the subgroup of patients with diabetes, ABGL > 200 mg/dl was an independent poor prognostic factor in terms of mortality at 30 and 90 (aOR 2.13, 95% CI 1.29–3.49 $p=0.003$, and 2.08 95% CI 1.39–3.11 $p<0.001$, respectively). ABGL > 200 mg/dl was also associated with in-hospital mortality (OR 1.84, $p=0.014$), though this association did not remain significant as per multivariable analysis (aOR = 1.56 95% CI 0.93–2.63) $p=0.09$) (Table 3). In patients with DM, elevated ABGL was not associated with worse morbidity outcomes. Among the 33 non-diabetic

Table 1 Characteristics of patients hospitalized with community-onset sepsis (08-12/2016), Shamir (Assaf Harofeh) Medical Center, Israel ($n=1527$)

	DM	Non-DM	Total	*p* value
Number (%)	469 (30.7)	1058 (69.3)	1527	
Demographics				
Age (years), median (IQR)	75 (66–83)	59 (34–78)	67 (43–81)	< 0.001
Female gender	211 (45.0)	649 (61.3)	860 (56.3)	< 0.001
Elderly (> 65 years old)	366 (78.0)	456 (43.1)	822 (53.8)	< 0.001
Background (prior to admission) medical statuses/conditions				
Dependent functional status	245 (52.2)	294 (27.8)	539 (35.3)	< 0.001
Altered consciousness[1]	120 (25.6)	152 (14.4)	272 (17.8)	< 0.001
Ischemic heart disease	182 (38.8)	141 (13.3)	323 (21.1)	< 0.001
Congestive heart failure	121 (25.8)	87 (8.2)	208 (13.6)	< 0.001
Peripheral vascular disease	69 (14.7)	38 (3.6)	107 (7.0)	< 0.001
Chronic kidney disease[2]	152 (32.4)	98 (9.3)	250 (16.4)	< 0.001
Chronic lung disease	109 (23.2)	168 (15.9)	277 (18.1)	0.001
Chronic pressure ulcer	44 (9.4)	39 (3.7)	83 (15.4)	< 0.001
Dementia	115 (24.5)	146 (13.8)	261 (17.1)	< 0.001
Cerebral vascular disease (TIA, CVA)	105 (22.4)	97 (9.2)	202 (13.2)	< 0.001
Active malignancy	43 (9.2)	98 (9.3)	141 (9.2)	0.953
Immunosuppressed[3]	66 (14.1)	153 (14.5)	219 (14.3)	0.842
Charlson's combined condition score[4]	7 (5–8)	2 (0–5)	4 (1–7)	< 0.001
Recent healthcare exposures				
HcAI per Duke 2002[5]	250 (53.3)	381 (36.0)	631 (41.3)	< 0.001
Any antibiotic course in the preceding 3 months	193 (42.6)	404 (39.8)	594 (40.1)	0.32
Invasive procedure in the preceding 6 months	84 (17.9)	149 (14.1)	233 (15.3)	0.06
Permanent device[6]	77 (16.4)	95 (9.0)	172 (11.3)	< 0.001
ICU stay in the preceding 3 months	7 (1.5)	6 (0.6)	13 (0.8)	0.077
Past MDRO[7] isolation in the preceding 2 years	89 (19.0)	94 (8.9)	183 (12.0)	< 0.001
Acute illness indices				
Severe sepsis/septic shock/multi-organ failure**	186 (39.7)	256 (24.2)	442 (29.0)	< 0.001
In an ICU at culture date	50 (10.7)	71 (6.7)	121 (7.9)	0.008
Ventilated at culture date	51 (10.9)	68 (6.4)	119 (7.8)	0.003
Acute kidney injury[8]	154 (35.2)	174 (16.7)	328 (22.2)	< 0.001
Altered consciousness at culture date	165 (35.2)	211 (19.9)	376 (24.6)	< 0.001
Clinical syndrome				
Urinary tract infection	120 (25.6)	249 (23.5)	369 (24.2)	0.388
Respiratory tract infection	168 (35.8)	384 (36.3)	552 (36.1)	0.859
Skin or soft-tissue infection	90 (19.2)	128 (12.1)	218 (14.3)	< 0.001
Microbiological and antimicrobial therapy				
Staphylococcus aureus BSI	11 (2.3)	9 (0.9)	20 (1.3)	0.018
MDRO infection	72 (15.4)	92 (8.7)	164 (10.7)	< 0.001
Klebsiella pneumoniae BSI	15 (1.0)	8 (1.7)	7 (0.7)	0.087
E. coli BSI	57 (3.7)	18 (3.8)	39 (3.7)	0.885
Appropriate therapy[9] given in < 48 h	105 (64.4)	253 (77.6)	358 (73.2)	0.002
Days to appropriate therapy,[9] median (range)	1.2 (0–10)	0.6 (0–7)	0.8 (0–10)	< 0.001

DM, diabetes mellitus, *IQR* interquartile range, *CVA* cerebrovascular accident, *TIA* transient ischemic attack, *HcAI*, healthcare-associated infection, *ICU* intensive care unit, *BSI*, bloodstream infection, *MDRO*, multi-drug resistant organism

[1]Altered consciousness includes also dementia and/or delirium

[2] Chronic kidney disease- glomerular filtration rate below 60 mL/min per 1.73 m^2 for 3 or more months

[3]Immunosuppressed includes neutropenia (< 500 neutrophils) at day of culture, steroid use for > 48 h in the past month, chemotherapy or radiotherapy in the past 3 months, HIV, bone marrow or solid organ transplantation and anti-TNF or anti-tyrosine kinase therapy in past 3 months

[4]Charlson's combined condition score- comorbidity measures calculated according to [50]

Table 1 (continued)

[5]Had at least one criterion of the Duke-2002 criteria for healthcare-associated infection [24]

[6]Permanent device for example -tracheotomies, tunneled central lines, silicon-based urinary catheters, orthopedic external fixators, implanted defibrillator, pacemaker, drains of any sort, GI/Urinary stoma

[7]past MDRO isolate- patient had MRSA, VRE, ESBL-producing Enterobacteriaceae (e.g., *Klebsiella* spp. *E. coli* or *Proteus mirabilis*), *Acinetobacter baumannii*, or *Pseudomonas aeruginosa*, or XDRs in the past 2 years

[8]Acute kidney injury- an increase in serum creatinine by ≥ 0.3 mg/dl within 48 h or an increase to ≥ 1.5 times the baseline value that is presumed to have occurred within the prior 7 days, or a decrease in urine volume to < 0.5 mL/kg/h over 6 h

[9]Appropriate therapy- per in-vitro susceptibilities

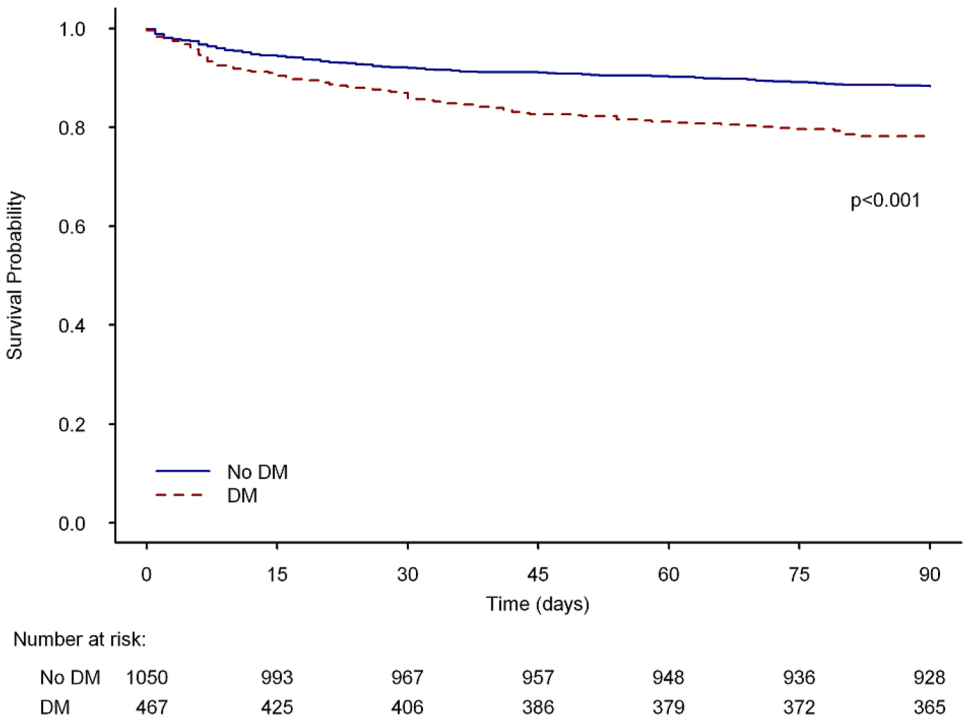

Fig. 1 Cumulative mortality in DM and non-DM patients with community-onset sepsis

patients, ABGL > 200 mg/dl were associated with increased 90-day mortality OR 2.34 (1.14–4.85) $p = 0.02$, though this association this did not remain independently associated as per multivariable analysis aOR 1.24 (0.6–2.55), $p = 0.55$.

Discussion

Sepsis is a common and deadly disease, and it is more common among diabetics [7]. However, the independent association of DM with worse sepsis outcomes is less established. The isolated association of elevated blood glucose levels at the onset of sepsis (even among non-diabetics), with the outcomes of sepsis, is not established as well. Previous investigations which queried the impact or independent statistical associations of DM with sepsis outcomes (i.e., both morbidity and mortality outcomes), had not executed strict criteria to control for established confounders, [5, 34] and have displayed conflicting results.[35, 36]. Differentiating between DM (as a chronic condition), and glucose levels as a modifiable prognostic factor (either as a causative factor or as a marker for severity of illness), could impact the management of sepsis and potentially improve patients' outcomes.

In this study, 1527 consecutive patients with community-onset sepsis upon admission to an acute-care hospital were enrolled. We included patients with 'community-acquired' and patients with 'healthcare-associated' infection [23] and excluded patients with 'hospital-acquired' infections since this is a distinct population with complex characteristics and features. As in previous studies [37, 38], in this large trial, diabetic patients with sepsis were much older and had more co-morbidities, with extensive exposures to healthcare settings. All these risk factors, including diabetes by itself [39], expose these patients, as indeed was evident in our cohort, to the risk of becoming MDRO carriers (Table 1). MDRO carriers are at increased risk for deleterious sepsis outcomes

Table 2 Hospitalization outcomes among patients with community-onset sepsis with and without diabetes

Mortality outcomes										
	DM	N-DM	HR (95% CI)	*p* value	(95% CI)	*p* value	aHR** (95% CI)	*p* value	aHR*** (95% CI)	*p* value
Mortality (90 d)	106 (22.6)	130 (12.3)	2.00 (1.54–2.6)	<0.001	1.14 (0.87–1.49)	0.35	1.13 (0.86–1.49)	0.37	0.99 (0.75–1.31)[a]	0.96
Mortality (30 d)	67 (14.3)	85 (8.0)	1.82 (1.32–2.51)	<0.001	1.14 (0.83–1.58)	0.41	1.1 (0.79–1.54	0.55	0.91 (0.65–1.28)[a]	0.61
Mortality (hospitalization)	63 (13.4)	79 (7.5)	1.28 (0.9–1.79)	0.14	1.16 (0.83–1.6)	0.38	1.21 (0.8–1.71)	0.29	0.92 (0.65–1.3)[b]	0.64
Morbidity outcomes (i.e., among survivors of the index hospitalization only)										
	DM	N-DM	OR (95% CI)	*p* value	aOR* (95% CI)	*p* value	aOR** (95% CI)	*p* value	aOR*** (95% CI)	*p* value
Functional deterioration	60 (14.8)	140 (10.1)	1.95 (1.36–2.78)	<0.001	1.17 (0.81–1.7)	0.39	1.1 (0.76–1.67)	0.54	1.06 (0.74–1.51)[c]	0.76
Discharge to LTCF[α]	25 (6.8)	85 (8.0)	1.82 (1.32–2.51)	0.03	1.03 (0.6–1.77)	0.91	0.87 (0.5–1.53)	0.63	1.0 (0.57–1.73)[d]	0.99
Additional hospitalization[β]	140 (39.4)	229 (21.6)	1.28 (0.9–1.79)	<0.001	1.46 (1.1–1.93)	<0.001	1.14 (0.84–1.54)	0.41	1.16 (0.92–1.48)[e]	0.21

DM diabetes mellitus, *N-DM no DM*, *HR* hazard ratio, *aHR* adjusted hazard ratio, *OR* odds ratio, *aOR* adjusted odds ratio, *PS* propensity score, *LTCF*, long-term care facility, *CHF* congestive heart failure, *CKD* chronic kidney disease, *PVD* peripheral vascular disease

*Adjusted for age, sex, dementia, clinical syndrome

**Adjusted for age, sex, dementia, bacterial growth and clinical syndrome

***PS adjusted:

[a]Adjusted for DM, age, sex, CHF, CKD, dementia, malignancy, Duke's criteria, positive culture, clinical syndrome, and bacterial growth

[b]Adjusted for DM, age, sex, CKD, dementia, malignancy, Duke's criteria, clinical syndrome, and bacterial growth

[c]Adjusted for DM, age, sex, CHF, dementia, malignancy and clinical syndrome

[d]Adjusted for DM, age, sex, CHF and dementia

[e]Adjusted for DM, age, sex, CHF, PVD, CKD, malignancy, Duke's criteria, clinical syndrome, and bacterial growth

[α]Only patients admitted from home

[β]In the following 3 months

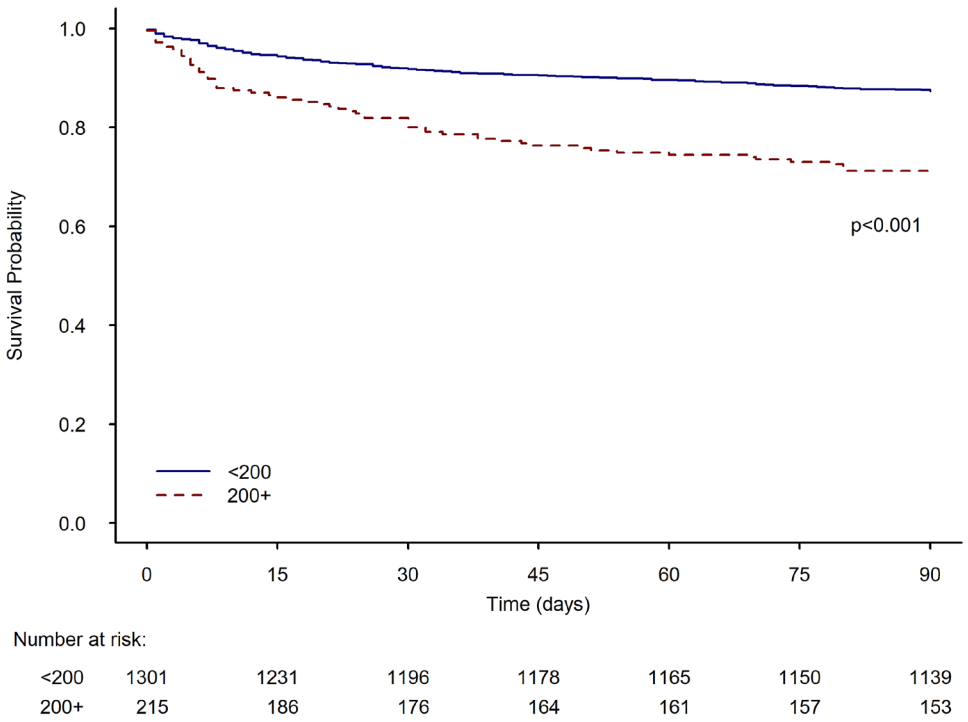

Fig. 2 Cumulative mortality in community-onset sepsis patients with admission blood glucose levels > 200 mg/dl and < 200 mg/dl

Table 3 Mortality outcomes in diabetic and non-diabetic patients according to blood glucose levels at admission

Whole study cohort									
	ABGL < 200 (n = 1311)	ABGL > 200 (n = 216)	p value	HR	p value	aHR*	p value	aHR**	p value
Mortality (90 d)	174 (13.3)	63 (29.2)	> 0.001	2.5 (1.87–3.36)	> 0.001	1.82 (1.36–2.44)	> 0.001	1.68 (1.24–2.27)	0.001
Mortality (30 d)	109 (8.3)	43 (19.9)	> 0.001	2.54 (1.78–3.62)	> 0.001	1.84 (1.29–2.62)	0.001	1.8 (1.12–2.58)	0.001
Mortality (hospitalization)	100 (7.6)	42 (19.4)	0.012	1.58 (1.1–2.29)	0.013	1.37 (0.95–1.98)	0.09	1.48 (1.02–2.16)	0.037
Patients with DM									
	ABGL < 200 (n = 286)	ABGL 200 < (n = 183)	p value	HR	p value	aHR*	p value	aHR**	p value
Mortality (90 d)	51 (17.8)	55 (30.1)	0.001	1.85 (1.26–2.72)	0.002	2.08 (1.39–3.1)	> 0.001	2.08 (1.39–3.11)	> 0.001
Mortality (30 d)	29 (10.1)	38 (20.8)	0.001	2.18 (1.34–3.53)	0.002	2.15 (1.31–3.53)	0.02	2.13 (1.29–3.49)	0.003
Mortality (hospitalization)	27 (9.4)	36 (19.7)	0.014	1.84 (1.19–3.04)	0.016	1.56 (0.93–2.63)	0.089	1.56 (0.93–2.63)	0.09
Patients without DM									
	ABGL < 200 (n = 1025)	ABGL 200 < (n = 33)	p value	HR	p value	aHR*	p value	aHR**	p value
Mortality (90 d)	123 (12)	8 (24.2)	0.016	2.34 (1.14–4.85)	0.02	1.24 (0.6–2.55)	0.55	1.08 (0.51–2.27)	0.83
Mortality (30 d)	80 (7.8)	5 (15.2)	0.1	2 (0.83–5)	0.157	1.09 (0.44–2.7)	0.85	0.99 (0.39–2.48)	0.99
Mortality (hospitalization)	73 (7.1)	6 (18.2)	0.9	0.94 (0.39–2.26)	0.9	0.7 (0.29–1.69)	0.43	0.7 (0.28–1.74)	0.44

ABGL, admission blood glucose levels, *HR*, hazard ratio, *aHR*, adjusted hazard ratio

*Adjusted for age, sex, dementia and clinical syndrome

**Adjusted for age, sex, dementia, bacterial growth and clinical syndrome

[40]. The detrimental impact of MDRO carriage on infectious outcomes is commonly due to delay in initiation of appropriate therapeutic management, which was also evident in this analysis (Table 1), and is considered the strongest modifiable independent mortality predictor in severe sepsis [41].

There is a complex interplay between diabetes and sepsis. During sepsis, dysregulated immune response influenced by both host and pathogen related factors is causing inflammation with a most deleterious effect [42]. Previous studies have suggested that both innate and adaptive immune systems are compromised in diabetic animals. The malfunction of neutrophils that is one of the reasons for worse outcome in diabetic patients with sepsis, may have a part in the lower incidence of ARDS, hence produce better outcomes in certain patients. The characteristics of the subpopulation of patients for whom diabetes can be a protective factor are unknown [15, 16]. This complexity can serve as an explanation for the mixing results of sepsis outcomes in diabetic patients in different studies. In this large trial, per bivariable analyses, there were significant associations between having DM and experiencing worse clinical outcomes of sepsis. However, these associations did not remain independently associated, as per multivariable analyses, with morbidity and mortality outcomes that were captured and analyzed (Table 2). The incorporation of well-controlled propensity score-matched analyses further weakened the statistical associations of diabetes per se, with worse outcomes of infections.

However, hyperglycemia (above 200 mg/dl) upon admission, was a strong independent prognostic predictor for mortality outcomes (Table 3). Stress hyperglycemia in sepsis, both among diabetics and non-diabetics, is a result of a complex interaction between counter-regulatory hormones and cytokines causing insulin resistance which leads to excess gluconeogenesis in the liver and reduced glucose uptake. The hyperglycemia itself causes inflammation and release of cytokines in a vicious cycle [29]. Stress hyperglycemia serves as a negative prognostic factor in other acute illnesses both infectious and non-infectious [43, 44]. In our cohort, elevated ABGL were associated with worse sepsis outcomes. In accordance with a previous study [45] and contrary to others [20, 37], hyperglycemia was associated with worse prognosis of sepsis more significantly in diabetics vs. non-diabetics (Table 3). This could be due to the small number of hyperglycemic non-diabetic patients in our cohort. Another explanation could be the relatively well-controlled diabetes of our diabetic patients. In previous studies, the lack of negative effect of hyperglycemia in diabetic patients was explained by the "diabetic paradox": uncontrolled diabetic patients with elevated HbA1c levels who are used to the hyperglycemic state, as opposed to well controlled patients with diabetes or non-diabetic patients, may tolerate stress induced hyperglycemia better [28, 46]. Diabetes care has improved globally over the years [47], reflected in the proportion of patients meeting the recommended goals for diabetes care, glycemic levels, daily glucose monitoring, routine podiatric care, and an increased rate of adherence to vaccination recommendations (e.g., influenza, *Streptococcus pneumoniae*). This is reflected in our relatively low HbA1c levels of the cohort (Supplementary Table 2). It is possible that among our well-controlled diabetic patients, the elevated ABGL represented true stress hyperglycemia as an indicator of sepsis severity, and not a marker of the uncontrolled diabetic state. This observation was also reported in previous studies [48, 49].

The study has several limitations. Its retrospective, chart-review based, single-center design, imposes multiple inherent confounders (such as lack of data regarding additional treatment modalities during hospitalization or socioeconomic status). However, this is a large cohort analysis, and we meticulously executed several methodologies to try and control for these confounders. We clearly isolated the independent impact of stress hyperglycemia on the outcomes of patients with community-onset sepsis. However, the pathophysiology, risk stratification, management, and therapeutic modalities of patients with sepsis and hyperglycemia, need to be further explored in future prospective controlled interventional investigations.

Funding The authors received no funding.

Compliance with ethical standards

Conflict of interest The authors have nothing to declare.

Ethical approval The study was approved by the local ethics (Helsinki) committee prior to its initiation.

Consent to participate Due to its retrospective nature no consent was necessary.

Consent for publication All authors give their consent for publication.

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