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Stress Hyperglycemia and Mortality in Subjects With Diabetes and Sepsis

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Objectives: Poor glycemic control is associated with mortality in critical patients with diabetes. The aim of the study was to assess the predicting value of stress hyperglycemia in patients with diabetes following hospital admission for sepsis.

Design: Retrospective observational study.

Setting: Adult, emergency department, and critical care in a district hospital.

Patients: In a 10-year retrospective analysis of sepsis-related hospitalizations in the emergency department, we carried out a secondary analysis of 915 patients with diabetes (males, 54.0%) in whom both fasting glucose at entry and glycosylated hemoglobin were available.

Interventions: None.

Measurements and Main Results: Patients' mean age was 79.0 (SD 11.0), glucose at admission was 174.0 mg/dL (74.3 mg/dL), and glycosylated hemoglobin was 7.7% (1.7%). Stress hyperglycemia was defined by the stress hyperglycemia ratio, that is, fasting glucose concentration at admission divided by the estimated average glucose derived from glycosylated hemoglobin. A total of 305 patients died (33.3%) in hospital. Factors associated with in-hospital case fatality rate were tested by multivariable logistic model. Ten variables predicting outcomes in the general population were confirmed in the presence of diabetes (male sex, older age, number of organ dysfunction diagnoses, in particular cardiovascular dysfunction, infection/parasitic, circulatory, respiratory, digestive diseases diagnosis, and Charlson Comorbidity Index). In addition, also glycemic control (glycosylated hemoglobin: odds ratio, 1.17; 95% CI, 1.15–1.40) and stress hyperglycemia (stress hyperglycemia ratio: 5.25; 3.62–7.63) were significant case fatality rate predictors. High stress hyperglycemia ratio (≥ 1.14) significantly increased the discriminant capacity (area under the receiver operating characteristic curve, 0.864; SE, 0.013; $p < 0.001$).

Conclusions: Stress hyperglycemia, even in the presence of diabetes, is predictive of mortality following admission for sepsis. Stress hyperglycemia ratio may be used to refine prediction of an unfavorable outcome.

Key Words: diabetes; emergency department; mortality; sepsis; stress hyperglycemia ratio

The high mortality rate for sepsis in the elderly population is fueled by several conditions, including multiple comorbidities, frailty, and repeated or prolonged hospitalizations (1, 2). In a large dataset covering all adult sepsis-related hospitalizations in an Italian District hospital in the period 2009–2016, diabetes was selected among variables able to predict mortality with good accuracy (3). Diabetes was very common in this frail and elderly population, accounting for nearly 30% of total cases (3).

The in-hospital mortality risk associated with diabetes in the elderly extends from sepsis (4) to comorbid conditions and cardiovascular risk (5), to drug-related hypoglycemia (6), and all factors fueled by poor glycemic control (7, 8). In the absence of diabetes, hyperglycemia at admission—stress-induced hyperglycemia, acute response to stress (9, 10)—may be even more ominous (11), increasing the risk of complications (12) and mortality (13).

The definition of stress hyperglycemia is a matter of discussion. Recently, Roberts et al (14) proposed relative hyperglycemia (also named stress hyperglycemia ratio [SHR]) as a tool to detect stress-induced hyperglycemia. SHR is defined by the ratio of admission glucose to the estimated average glucose derived from glycated hemoglobin [HbA1c]). As such, SHR, controlling for background glycemic control, proved valid to detect an abnormal response also

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in the presence of diabetes. The marker has been shown to be a better correlate of critical illness than absolute hyperglycemia (14), predicting negative outcomes in the elderly in several recent studies (12, 15, 16), particularly in the surgical setting (17–19).

We performed a specific analysis on predictors of case fatality rate (CFR) in the cohort of subjects with diabetes enrolled in our district hospital database on sepsis-associated admissions (3). The aim of the study was to verify if relative hyperglycemia, measured by SHR also drives in-hospital CFR in this specific setting.

MATERIALS AND METHODS

Study Design

In a chart review analysis, we included all adults with sepsis-related hospital admission to the District hospital of Forlì (FC), Italy, from 2009 to 2018, as defined by Singer et al (20). The present cohort is an extension of a previously reported database, updated to 2018 and limited to subjects with a diagnosis of diabetes at entry (3). In emergency department (ED), an electronic warning system is available (systemic inflammatory response syndrome [SIRS]) (21) for the early detection of patients at high risk of sepsis since 2007. The final diagnosis was derived from hospital discharge codes (see below).

Registry Data

The community hospital has a total capacity of 463 beds; during the 10-year study period, over 70,000 cases were hospitalized after ED visits for surgical and medical diseases out of 212,000 admissions. The hospital database is directly connected with the General Registry Office of the District.

Patients

The study included any subject with *International Classification of Diseases*, 9th Edition, Clinical Modification (ICD-9-CM) code for both bacterial and fungal infections and acute organ dysfunction with a code extraction method according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (22, 23). As the study period predated the 2016 definitions (20), sepsis patients were defined by the above criteria, as previously suggested (24, 25). In order to include all cases, we also included cases explicitly coded as severe sepsis (995.92) or septic shock (785.52). This approach was accepted as compatible with the Sepsis-3 (23).

All information extracted by diagnosis codes were matched with data recorded at ED arrival, also in cases without a suspected diagnosis of sepsis at the time of ED presentation.

Data Variables

The variables recorded for analyses included demographic characteristics, main comorbid conditions, the codes of serious infection diagnoses and organ dysfunction diagnoses, and SIRS score greater than or equal to 2 at entry. Data abstractors identified up to five documented diagnoses for each patient by ICD-9-CM codes. For this specific study, three additional parameters were considered: blood glucose, HbA1c, and SHR at admission. SHR was calculated by dividing the fasting glucose concentration by the estimated average glucose derived from HbA1c, assessed by the equation: estimated average glucose (mg/dL) = (28.7 × HbA1c [%])–46.7 (26). Stress hyperglycemia was defined by SHR greater than or equal to 1.14 (16).

In-hospital CFR (i.e., the proportion of all-cause mortality) was verified by a linked local death certificate database and considered for the prognostic model.

Statistical Analysis

The characteristics and outcomes of patients were compared across the 10-year study period (January 2009 to December 2018). Mean value, SD, median, interquartile range, number of cases, and percent with 95% CI were used to describe data distribution. Fisher exact test and Student *t* test were used to compare categorical and continuous variables between groups.

A multivariable model was developed by stepwise forward analysis of factors significant in univariable analysis and according to clinically relevant predictors. For the model building part of the analysis, the variables were selected on the basis of previous reports and a putative association with main outcome measures, in particular CFR. The full list of covariates can be found in **Tables 1** and **2**. The following variables were tested as independent parameters, having mortality as outcome: age, sex, SIRS at entry, length of ED stay, diagnosis codes of serious infection and organ dysfunction, and Charlson Comorbidity Index (22), calculated on the basis of the main comorbidities, in particular chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), history of acute heart failure (AHF), dementia, cancer, and HIV infection. Finally, also HbA1c and SHR (dichotomized as below or ≥ 1.14) were included. Data were expressed as odds ratio (OR) and 95% CI.

Colinearity was tested by the variation inflation factor (< 2, not significant). A score for risk of mortality was calculated for each patient on the basis of the coefficients computed by the logistic regression derived from variables entering the stepwise procedure. The accuracy of the scoring system was determined by calculating the area under the receiver operating characteristic (AUROC) curve with SE.

The IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY) was used in statistical analyses.

Ethics

The study was approved by the ethical committee of Comitato Etico della Romagna, Romagna, Italy (2299/2019/O/OssN, January 16, 2019). The permission to access the medical records, considering the observational and retrospective nature of the study, was conducted on anonymized records (Privacy guarantor act, GU March 1, 2012, n. 72).

RESULTS

The study population included 915 patients (494 male subjects, 54.0%): their mean age was 79.0 (SD, 11.0). The clinical profile of patients in relation to low (< 1.14) or high SHR (≥ 1.14) classes is summarized in Table 1. Main comorbidities were COPD (42.2%), AHF (40.7%), CKD (38.4%), cancer (35.6%), and dementia (32.2%), with high dementia and cancer more represented in the group of patients with high SHR (Table 1).

The most common serious infection diagnoses involved the respiratory system (58.9%), infection/parasitic diseases (42.4%), and the genitourinary tract (26.2%); they all were more represented in subjects with high SHR (Table 2).

TABLE 1. Characteristics of Patients With Diagnosis of Sepsis and Diabetes

Characteristics	All Cases ($n = 915$)	SHR < 1.14 ($n = 610$)	SHR ≥ 1.14 ($n = 305$)	OR (95% CI)	*p*
Sex (male %)	494 (54.0)	326 (53.4)	168 (55.1)	1.07 (0.81–1.41)	0.673
Age (yr)	79.0 (11.0)	77.3 (11.3)	82.3 (10)		0.080
Comorbidities					
Chronic obstructive pulmonary disease	386 (42.2)	251 (41.4)	135 (43.8)	1.14 (0.86–1.45)	0.394
Acute heart failure	372 (40.7)	236 (38.7)	136 (44.6)	1.27 (0.96–1.68)	0.087
Chronic kidney disease	351 (38.4)	224 (36.7)	127 (41.6)	1.23 (0.93–1.63)	0.150
Dementia	295 (32.2)	169 (27.7)	126 (41.3)	1.84 (1.38–2.45)	< 0.001
Cancer	326 (35.6)	197 (32.3)	129 (42.3)	1.54 (1.16–2.04)	0.003

OR = odds ratio, SHR = stress hyperglycemia ratio.
Subjects were divided in relation to (< 1.14) and high (≥ 1.14) SHR values. Data are reported as number of cases and (percent) and mean (SD).

The more frequently observed organ/system dysfunction diagnoses involved the pulmonary (51.4%), cardiovascular (34.1), and renal system (22.0%), with cardiovascular dysfunction more represented in subjects with high SHR (56.1% vs 23.1%; OR, 4.24; 95% CI, 3.16–5.79; $p < 0.001$) (Table 2).

Charlson Comorbidity Index greater than or equal to 5 was observed in 647 of 915 cases (70.7%); it was recorded in 252 subjects in the high SHR cohort versus 53 among the low SHR cases (82.6% vs 17.4% of total; $p < 0.001$).

Among the parameters of glucose metabolism, fasting glucose was 174 mg/dL (74 mg/dL) (mean [SD]), HbA1c was 7.7% (1.7%), and SHR was 1.0 (0.36).

Hospital stay averaged 16 days (20 d) and 15 days (20 d) in subjects with high and low SHR, respectively ($p = 0.967$). Overall, 336 patients died in hospital (36.7%) after a mean period of stay of 6 days (13 d) in high SHR and 8 days (18 d) in low SHR ($p = 0.863$). Mortality was nearly doubled in subjects (62.8%) with SHR greater than or equal to 1.14 compared with subjects with SHR less than 1.14 (37.2%) (OR, 8.71; 95% CI, 6.37–11.91; $p < 0.001$).

In the logistic model 10 items, out of the 21 tested, entered as outcome predictors (**Table 3**), including both HbA1c, a measure of glycemic control, and SHR, that increased the risk of mortality by over five times. Analytical and graphical methods showed that the proportionality assumption of the model was not violated (not

TABLE 2. Serious Infection and Organ Dysfunction Diagnoses in Subjects With Diabetes in Relation to Stress Hyperglycemia Ratio Categories

Variables	All Cases ($n = 915$)	SHR < 1.14 ($n = 610$)	SHR ≥ 1.14 ($n = 305$)	OR (95% CI)	*p*
Serious infection diagnosis					
Respiratory system	539 (58.9)	339 (55.6)	200 (65.6)	1.52 (1.14–2.02)	0.004
Infection/parasitic	388 (42.4)	241 (39.5)	147 (48.2)	1.42 (1.08–1.88)	0.013
Genitourinary system	240 (26.2)	147 (24.1)	93 (30.5)	1.38 (1.02–1.88)	0.046
Digestive system	91 (9.9)	53 (8.7)	38 (12.5)	1.50 (0.96–2.33)	0.079
Circulatory system	52 (5.7)	33 (5.4)	19 (6.2)	1.16 (0.65–2.08)	0.650
Nervous system	31 (3.4)	20 (3.3)	11 (3.6)	1.10 (0.52–2.33)	0.847
Other	65 (7.1)	42 (6.9)	23 (7.5)	1.10 (0.65–1.87)	0.785
Organ dysfunction diagnosis					
Pulmonary	470 (51.4)	325 (53.3)	145 (47.5)	0.79 (0.60–1.05)	0.107
Cardiovascular	312 (34.1)	141 (23.1)	171 (56.1)	4.24 (3.16–5.70)	< 0.001
Renal	201 (22.0)	135 (22.1)	66 (21.6)	0.97 (0.70–1.35)	0.933
Neurologic	30 (3.3)	22 (3.6)	8 (2.6)	0.72 (0.32–1.64)	0.556
Hematologic	25 (2.7)	18 (3.0)	7 (2.3)	0.77 (0.32–1.87)	0.670
Hepatic	18 (2.0)	13 (2.1)	5 (1.6)	0.76 (0.27–2.17)	0.802

OR = odds ratio, SHR = stress hyperglycemia ratio.

TABLE 3. Predictors of Mortality in Diabetic Subjects Following Diagnosis of Sepsis-Related Hospitalizations by Variables Included in the Logistic Model

Variables	OR (95% CI)	*p*
Cardiovascular dysfunction	4.02 (2.52–6.43)	< 0.001
Circulatory system diseases	3.96 (1.89–8.30)	0.001
Respiratory system diseases	3.92 (2.24–6.86)	< 0.001
Digestive system diseases	3.27 (1.73–6.20)	< 0.001
Number of organ dysfunction	1.64 (1.16–2.32)	0.006
Age ≥ 80 yr	2.64 (1.74–4.01)	< 0.001
Infectious/parasitic diseases	2.93 (1.70–5.05)	< 0.001
Charlson Comorbidity Index	1.88 (1.17–3.03)	0.009
Glycated hemoglobin	1.27 (1.15–1.40)	< 0.001
Stress hyperglycemia ratio ≥ 1.14	5.25 (3.62–7.63)	< 0.001

OR = odds ratio.

Variables not included in the model: sex, systemic inflammatory response syndrome score at entry, genitourinary, hematologic, neurologic, other diseases diagnosis, number of serious infections, hepatic, hematologic, respiratory, and neurologic dysfunction diagnoses. Data are reported as OR and 95% CIs.

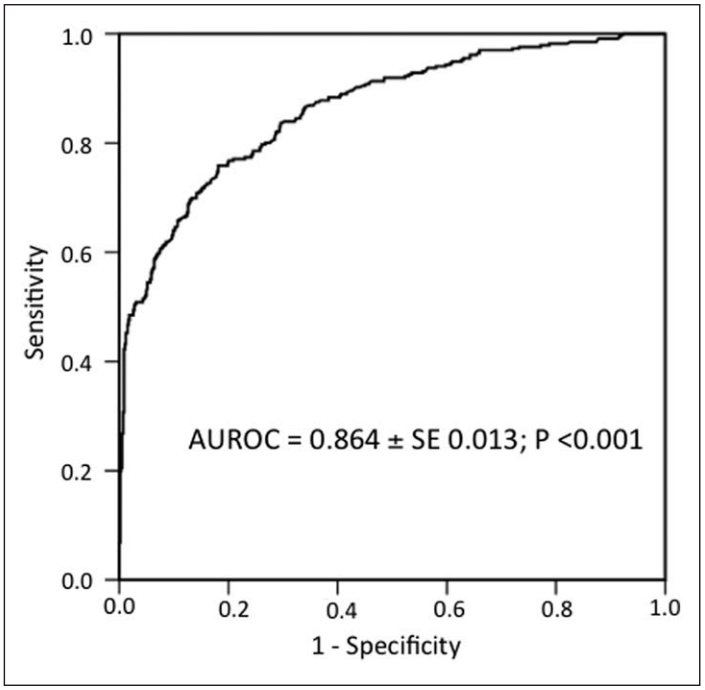

Figure 1. Nonparametric area under the receiver operating characteristic (AUROC) plots of the risk score obtained by logistic regression in identifying case fatality rate of subjects with sepsis and diabetes.

reported in details) and the final model showed an overall accuracy (AUROC curve, 0.864; SE, 0.013; $p < 0.001$) (**Fig. 1**).

In a sensitivity analysis, SHR was also used as continuous variable in the outcome prediction model and similarly entered the regression (OR, 9.52 per one-point increase; 95% CI, 5.60–16.19).

DISCUSSION

In elderly patients with sepsis and diabetes admitted to a general hospital, the study confirms the role of several, previously identified demographic and clinical variables in predicting outcome, but adds both glycemic control and stress hyperglycemia as significant risk factors of poor outcome.

A role of glycemic control was largely expected. Poor control has consistently been reported to increase the risk of infections and cardiovascular outcomes in both type 1 (27) and type 2 (28) diabetes, compared with tight control. The risk might be mediated by the ominous effect of poor glycemic control on immune function and is corrected by intensive insulin administration to target (4). Real world evidence in primary care settings confirmed the risk for sepsis-associated both with diabetes per se and with glycemic control within the diabetes cohort (29), and the same was true in subpopulations with comorbid conditions (30). A recent reappraisal of the problem in over 85,000 patients with diabetes confirmed the long-term risk associated with increasing HbA1c for most outcomes and specifically for infection, with poor control accounting for 21% of attributable fraction of sepsis, 17% of infection-related hospital admission, and 16% of mortality (31). In the presence of sepsis HbA1c was reported as independent predictor of in-hospital mortality (OR, 1.36), together with female sex (OR, 2.24), Acute Physiology and Chronic Health Evaluation (APACHE) II score (OR, 1.08), and Sequential Organ Failure Assessment score (OR, 1.28) (32). The importance of glycated hemoglobin was confirmed in a community-based study from Taiwan (33), in a different hospital-based population, where diabetes-related complications were the most common death risks (34).

The role of stress hyperglycemia is less clearly defined, particularly in the presence of diabetes, also considering the uncertainty of its assessment. In subjects without a diabetes history, the presence of elevated blood glucose during stressful conditions might indicate stress hyperglycemia, but the possibility of recent-onset, unknown diabetes is not excluded. For this reason, Roberts et al (14) proposed SHR, that is, admission glucose divided by the estimated average glucose derived from HbA1c as a tool to detect stress hyperglycemia. By controlling for background blood glucose, SHR was reported to be a better biomarker than absolute hyperglycemia, although the cutoff value to define stress hyperglycemia has never been convincingly validated. The value of 1.14, used in the present study, has previously been used in subjects with diabetes submitted to orthopedic surgery, where it confirmed a prognostic value (16), but the critical value to define stress hyperglycemia remains poorly defined. In the original study by Roberts et al (14), a significant increase in mortality was specifically observed in the fourth and fifth SHR quintile, corresponding to average SHR values of 1.14 and 1.38, respectively. In subject with coronary heart disease, Yang et al (35) found an increased mortality risk in the upper SHR quartile of the population; the authors do not provide the exact cut point, but the dichotomized population had a mean value of 0.85 ± 0.15 (quartiles 1–3) versus 1.38 ± 0.32 (quartile 4). Other studies tested SHR as continuous variable (36); in a large

series of critical patients, the median SHR in survivors was 1.10 (interquartile range, 0.89–1.35) and as high as 1.34 (1.02–1.84) in patients who died. The cutoff we choose seems a reasonable and conservative compromise to indicate the presence of stress hyperglycemia. Considering the average blood glucose of the whole population (174 mg/dL), the SHR value of 1.14 turns into an average blood glucose excess of 25 mg/dL above the one predicted by HbA1c.

According to the selected cutoff, the presence of stress hyperglycemia increases the risk of mortality by over five times. In a study from Thailand, stress hyperglycemia in patients with sepsis (42.3% of total cohort) was not associated with specific clinical data and interventions, compared with no-stress hyperglycemia, and did not affect mortality (37). On the contrary, in critically ill patients with diabetes in an ICU setting, stress hyperglycemia, measured by the glycemic gap (in mg/dL compared with glycemia expected on the basis of HbA1c) significantly improved the discriminative performance for mortality when added to APACHE II score, increasing AUROC from 0.755 to 0.794 ($p < 0.001$) (38). Notably, very recently, Lee et al (36) confirmed that the addition of SHR to APACHE II score minimally but significantly outperforms in predicting in-hospital mortality in critically ill patients admitted to a mixed medical-surgical intensive care (AUROC increasing from 0.771 to 0.782; $p = 0.014$). SHR was significantly associated with mortality in multivariate analysis, both in subjects without diabetes (HbA1c < 6.5%) and in the presence of diabetes (HbA1c ≥ 6.5%; OR = 1.08 per 0.1 SHR increment). This value is in fairly good agreement with the OR, we found of 9.6 per one-point increment in SHR.

In our setting, the two cohorts with SHR below and above the discriminant cutoff 1.14 differed for a few important characteristics. A different prevalence of respiratory, genitourinary, and other infections (approximately 1.4–1.5×) and cardiovascular dysfunction (over 4×) were recorded among system of serious infection and clinical dysfunction diagnoses. The importance of stress hyperglycemia in the occurrence of cardiovascular events was recently confirmed in a surgical setting, where SHR was systematically associated with both infections and cardiovascular events in the presence of diabetes (16).

The study has both strengths and limitations. The main strengths are the large single-center dataset, which guarantees strict adherence to diagnostic criteria and the single laboratory used for blood glucose and HbA1c analysis. Admission blood glucose was considered, not blood glucose in the course of the in-hospital stay, which might vary considerably during hospital stay. The main limitation is the lack of data in subjects without diabetes, where HbA1c was not collected; such records might be used to define the possible role of isolated stress hyperglycemia, as well as to confirm the advantage of SHR over hyperglycemia in detecting the stress-induced glycemic imbalance. An additional limitation, particularly in the elderly and frail population, might be the presence of severe kidney disease with anemia, invalidating the use of HbA1c as index of glycemic control. This bias would lead to an overestimation of stress hyperglycemia and to false positive cases, likely to dilute the effect of true stress-induced alterations on mortality.

CONCLUSIONS

In summary, our analysis identifies stress-induced hyperglycemia as a relevant prognostic factor also in the presence of diabetes. Mild-to-moderate stress hyperglycemia is considered a protective reaction to providing fuel for the immune system and brain at a time of stress; however, the additional hyperglycemia and insulin resistance it creates may be potentially deleterious (39) directly contributing to adverse outcomes via endothelial dysfunction, increased free radical production (oxidative stress), inflammatory responses, and vascular and immune dysfunction (40). In recent studies, we found that immediate treatment of hyperglycemia by basal-bolus insulin injection, irrespective of the presence of diabetes, reduced adverse events, and septic complications in surgical patients (41). To improve outcomes of critical elderly patients, adequate treatment of hyperglycemia may be systematic implemented also in ED, in keeping with the results observed in ICUs (42).

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Dr. Fabbri had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the results, and he takes responsibility for the article as a whole. Drs. Benazzi, Morelli, and Bini were responsible for collection, management, analyses, and interpretation of the data. Drs. Fabbri, Marchesini, Montesi, and Rizzo conducted the statistical analyses and drafted the article. All authors were involved in the study concept, design, and statistical analyses. All authors contributed substantially to its revision and agree to be accountable for all the aspects of the work.

The authors have disclosed that they do not have any potential conflicts of interest.

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