Received: 31 August 2023 | Revised: 26 November 2023 | Accepted: 1 December 2023

DOI: 10.1002/emp2.13091

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
Open Access
WILEY

ORIGINAL RESEARCH

Evidence-Based Emergency Medicine

# Association of preclinical blood glucose with hospitalization rate and in-hospital mortality: A single-center retrospective cohort study

Simon Kloock MD[1] | Danilo Skudelny[2] | Peter Kranke MD[3] | Gülmisal Güder MD, PhD[2] | Dirk Weismann PhD[4] | Martin Fassnacht MD[1] | Christian Ziegler PhD[1,5] | Ulrich Dischinger MD, PhD[1]

[1]Department of Internal Medicine, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany

[2]Department of Internal Medicine, Division of Cardiology, University Hospital, University of Würzburg, Würzburg, Germany

[3]Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital, University of Würzburg, Würzburg, Germany

[4]Department of Internal Medicine, Intensive Care Unit, University Hospital, University of Würzburg, Würzburg, Germany

[5]Department of Internal Medicine III, University Hospital Carl Gustav Carus Dresden, Dresden, Germany

**Correspondence**
Ulrich Dischinger, Department of Internal Medicine, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany.
Email: Dischinger_U@ukw.de

Partial or complete datasets and data dictionary are available upon request to Dr Ulrich Dischinger at dischinger_u@ukw.de, to investigators who provide an institutional review board letter of approval.

**Funding and support:** By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

## Abstract

**Objective:** Critical illness is often accompanied by elevated blood glucose, which generally correlates with increased morbidity and mortality. Prehospital blood glucose (PBG) level might be a useful and easy-to-perform tool for risk assessment in emergency medicine. This retrospective single-center cohort study was designed to analyze the association of prehospital glucose measurements with hospitalization rate and in-hospital mortality.

**Methods:** Records of 970 patients admitted to a university hospital by an emergency physician were analyzed. Patients with a PBG ≥140 mg/dL (G1, $n$ = 394, equal to 7.8 mmol/L) were compared with patients with a PBG <140 mg/dL (G2, $n$ = 576). Multivariable logistic regression models were used to correct for age, prediagnosed diabetes, and sex.

**Results:** Five hundred thirty-four patients (55%) were hospitalized. In comparison to normoglycemic patients, hyperglycemic patients were more likely to be hospitalized with an adjusted odds ratio (OR) of 1.48 (95% confidence interval [CI] 1.11–1.97), more likely to be admitted to the intensive care unit (ICU) with an adjusted OR of 1.74 (95% CI 1.31–2.31) and more likely to die in the hospital with an adjusted OR of 1.84 (95% CI 0.96–3.53). Hospitalized hyperglycemic patients had a median length of stay of 6.0 days (interquartile range [IQR] 8.0) compared to 3.0 days (IQR 6.0) in the

Supervising Editor: Marna Rayl Greenberg, DO, MPH

normoglycemic group ($P < 0.001$). In the subgroup analysis of cases without known diabetes, patients with PBG ≥140 mg/dL were more likely to be hospitalized with an adjusted OR of 1.49 (95% CI 1.10–2.03) and more likely to be admitted to ICU/intermediate care with an adjusted OR of 1.80 (95% CI 1.32–2.45), compared to normoglycemic patients.

**Conclusion:** Elevated PBG ≥140 mg/dL was associated with a higher hospitalization risk, a longer length of stay, and a higher mortality risk and may therefore be included in risk assessment scores.

KEYWORDS
diabetes, emergency medicine, glucose, patient outcome, prehospital care, stress hyperglycemia

# 1 | INTRODUCTION

## 1.1 | Background

Stress hyperglycemia (SH) is a frequent finding in patients assigned to emergency departments or ICUs.[1–3] It correlates with higher in-hospital morbidity, length of stay, and mortality.[4] Poorer outcomes associated with SH have been reported for myocardial infarction and stroke but also in viral infections like COVID-19.[5–9] Therefore, it has been proposed that blood glucose should be regarded as a vital sign and should be measured on a regular basis in emergency medicine.[10] The exact mechanisms for developing SH are not fully elucidated. Most likely, this metabolic state is caused by a combination of multiple conditions ultimately leading to increased gluconeogenesis and elevated hormone levels of glucagon, cortisol, and catecholamines, which results in insulin-resistance and elevated blood glucose.[11,12] In addition, acute stress causes inflammation, which also leads to elevated blood glucose levels, at least partly through a further activation of the hypothalamic–pituitary–adrenal (HPA) axis.[12–14] Although it is unclear how cytokines penetrate the blood–brain barrier and reach corticotropin-releasing hormone (CRH)-expressing neurons of the hypothalamus, it is undisputed that tumor necrosis factor $\alpha$ (TNF-$\alpha$), interleukin-1 (IL-1), and interleukin-6 (IL-6) have stimulating effects on the HPA-axis. Additionally, hyperglycemia itself can trigger the production of proinflammatory cytokines like TNF-$\alpha$, IL-1, and IL-6[13,15] and impair antigen presentation at macrophages, monocytes, and neutrophilic granulocytes.[15–17] Therefore, a vicious circle arises (see Figure 1), ultimately leading to a procoagulatory state[18,19] and an increased risk of cardiovascular events with increased mortality.[20,21]

## 1.2 | Importance

Hyperglycemia is more frequent in patients with known diabetes mellitus, but higher blood glucose levels were associated with a greater mortality risk in non-diabetic patients as well.[5] Remarkably, the mortality risk in patients with myocardial infarction was even higher in hyperglycemic patients who were not prediagnosed with diabetes mellitus, compared to patients with known diabetes.[5,21,22]

## 1.3 | Goals of this study

The aim of this study was to analyze the relevance of prehospital blood glucose (PBG) levels for the outcome of patients admitted to an ED. The main objectives were hospitalization rate and in-hospital mortality. We hypothesize that prehospital detection of elevated glucose may be another indicator to predict clinical outcome and could therefore be included in risk assessment scores.

# 2 | METHODS

## 2.1 | Study design

This single-center retrospective cohort study was carried out at the medical emergency unit of the University Hospital of Wuerzburg (Germany). The observation period of 1 year started from January 1, 2020 and lasted until December 31, 2020.

## 2.2 | Setting

All patients admitted to the hospital by an emergency physician were enrolled; patients admitting themselves to the ED were not included in this study. The German emergency medicine service is physician based, and paramedics support the emergency physician. Preclinically, the specially trained emergency physician examines the patient and decides whether a further clinical treatment is necessary. According to German law, the emergency physician generates a hand-written report including vital signs, initial symptoms and clinical findings. Blood glucose is routinely measured in the field by point-of-care testing (POCT) using hand-held glucose meters. The decision whether a patient is to be discharged directly from the emergency unit or to be hospitalized is made by the emergency doctor at the hospital.

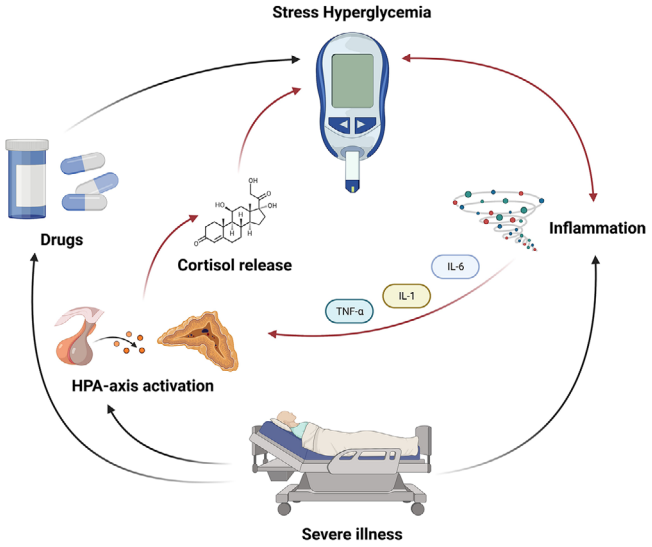


**FIGURE 1** Potential vicious circle in severely ill patients with stress hyperglycemia. Severe illness leads to an activation of the HPA-axis and to the release of cortisol and other adrenal hormones (like catecholamines). Medical treatments (like parenteral nutrition or exogenous glucocorticoids and catecholamines) further aggravate hyperglycemia. Critical illness promotes inflammation, which is further aggravated by hyperglycemia and leads to a persistent release of glucose-releasing hormones. Image created with BioRender.com. Abbreviations: HPA, hypothalamic–pituitary–adrenal; IL, interleukin; TNF-$\alpha$, tumor necrosis factor alpha.

## 2.3 | Selection of participants

A total of 1418 adult patients were admitted to the department of internal medicine (see flow chart Figure S1). PBG was measured in 1059 patients. Patients with hypoglycemia (blood sugar <60 mg/dL) were excluded ($n$ = 12; mostly caused by insulin overdosing). Predefined exclusion criteria were applied to eliminate confounders that are per se associated with a worsened prognosis and increased mortality: Patients were excluded due to prehospital intubation, ventilation, and end-stage disease ($n$ = 64) or preclinical resuscitation and defibrillation ($n$ = 13). The remaining 970 patients were further characterized.

## 2.4 | Measurements

Blood glucose, vital signs, and initial symptoms were derived from the emergency reports (multiple symptoms per case are possible). Further data (eg, blood values, duration of stay, etc.) were obtained from the hospital information system software. Further variables were age, sex, the most common initial symptoms, preclinical vital signs including preclinical ECG (if available) and selected initial blood values of relevance in emergency medicine. In the literature, cutoffs for hyperglycemia are not uniform. In this study, a cutoff of ≥140 mg/dL (equal to 7.8 mmol/L) was used, according to the American Association of Clinical Endocrinologists and American Diabetes Association's definition for hyperglycemia in hospitalized patients.[8,23–25] Patients were separated into 2 groups: those with elevated PBG ≥140 mg/dL (G1, $n$ = 394) and those without elevated PBG <140 mg/dL (G2, $n$ = 576). A subgroup analysis depending on the condition of prediagnosed diabetes was performed. Using the same PBG cutoff of 140 mg/dL, a group of diabetic patients with elevated PBG ≥140 mg/dL (D1, $n$ = 125) was separated from a group of diabetic patients with non-elevated PBG <140 mg/dL (D2, $n$ = 36) and a group of non-diabetic patients with elevated (ND1, $n$ = 269) was separated from a group of non-diabetics with non-elevated PBG (ND2, $n$ = 540), respectively.

**The Bottom Line**

An elevated prehospital blood glucose ≥ 140 mg/dL increases the risk for hospitalization by 48%, the risk for ICU admission by 74%, and the risk to die in hospital by 84% in an adult patient cohort in an internal medicine emergency unit. Detection of elevated prehospital blood glucose might be an indicator of a worse outcome, which could be used in scoring systems.

## 2.5 | Outcomes

The primary outcomes were hospitalization, ICU/intermediate care (IMC) admission, length of stay, and in-hospital mortality.

## 2.6 | Data analysis

Statistical analysis was performed using Jamovi (V.2.3.26), SPSS (V.29.0.0.0), and GraphPad Prism (V.9). Baseline descriptive statistics were reported with mean and SD or median and interquartile range (IQR), where appropriate. Normal distribution was tested using the Shapiro–Wilk-test. Statistical testing was carried out using chi-square-test and Mann–Whitney $U$-test, where appropriate, results were reported as $P$ values or odds ratio (OR) with 95% confidence interval (CI). Multivariable logistic regression models were used to compute adjusted ORsand $P$ values (analysis of covariance) adjusted for age, prediagnosed diabetes, and sex. Non-parametric correlation was analyzed using Spearman's rank correlation coefficient. To visualize the association of PBG with hospitalization rate and PBG with in-hospital mortality, the data were transformed using restricted cubic splines (with 5 knots) and was plotted side -by side with the respective frequency distribution (to allow a comparison with the overall PBG frequency distribution available in Figure S2). A $P$-value <0.05 was regarded as significant.

## 2.7 | Ethics approval

The study protocol was approved (file no. 2020012901) by the ethics committee of the University of Wuerzburg, Wuerzburg, Germany (Chairperson Prof. Dr. Bröcker) on March 4, 2020.

**TABLE 1** Baseline characteristics of initial symptoms, preclinical vital signs, and blood values for all patients.[a]

| | All patients ($n = 970$) | G1 ($n = 394$) | G2 ($n = 576$) | *P* value |
|---|---|---|---|---|
| PBG (mg/dL) – median (IQR) | 130 (49) | 169 (54.8) | 115 (22.0) | **<0.001** |
| Age—median (IQR) | 67 (25) | 72 (20) | 63 (31) | **<0.001** |
| Male sex—*n* (%) | 510 (52.6%) | 223 (56.6%) | 287 (49.8%) | **0.038** |
| *Initial symptoms preclinically* | | | | |
| Chest pain—*n* (%) | 300 (30.9%) | 115 (29.2%) | 185 (32.1%) | 0.332 |
| Dyspnea—*n* (%) | 160 (16.5%) | 72 (18.3%) | 88 (15.3%) | 0.217 |
| Nausea—*n* (%) | 111 (11.4%) | 41 (10.4%) | 70 (12.1%) | 0.401 |
| Vertigo—*n* (%) | 91 (9.4%) | 35 (8.9%) | 56 (9.7%) | 0.660 |
| Syncope/orthostasis—*n* (%) | 103 (10.6%) | 53 (13.4%) | 50 (8.7%) | **0.018** |
| Accident/fall—*n* (%) | 21 (2.2%) | 13 (3.3%) | 8 (1.4%) | **0.045** |
| *Preclinical vital signs* | | | | |
| Oxygen saturation – median (IQR) | 97 (4.0) | 96 (6.0) | 97 (4.0) | **<0.001** |
| Heart rate – median (IQR) | 88 (37.0) | 90 (40.3) | 86 (31.0) | **0.012** |
| Systolic blood pressure – median (IQR) | 145 (50.0) | 144 (57.3) | 147 (40.0) | 0.063 |
| GCS – median (IQR) | 15 (0.0) | 15 (0.0) | 15 (0.0) | 0.120 |
| ECG with normal sinusrhythm – *n* of available ECGs (%) | 560 of 813 (68.9%) | 201 of 327 (61.5%) | 359 of 486 (73.8%) | **<0.001** |
| *Initial in-hospital blood results* | | | | |
| Sodium (mmol/L) – median (IQR) | 140 (4.0) | 139 (4.0) | 140 (4.0) | **0.001** |
| Potassium (mmol/L) – median (IQR) | 4.2 (0.6) | 4.2 (0.6) | 4.2 (0.6) | 0.092 |
| Glucose (mg/dL) – median (IQR) | 120 (50.0) | 157 (67.3) | 108 (26.0) | **<0.001** |
| Leukocytes (1/$\mu$L) – median (IQR) | 8.4 (4.2) | 9.4 (5.2) | 7.9 (3.5) | **<0.001** |
| Hemoglobin (g/dL) – median (IQR) | 13.2 (2.5) | 13.0 (2.8) | 13.3 (2.3) | **0.002** |
| C-reactive protein (mg/dL) – median (IQR) | 0.5 (1.6) | 0.6 (2.0) | 0.4 (1.1) | **<0.001** |

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; IQR, interquartile range.
Significant *p* values printed in bold.
[a]G1 (PBG ≥140 mg/dL) and G2 (PBG <140 mg/dL). Statistical testing was performed using chi-square-test and Mann–Whitney *U*-test, where appropriate.

## 3 | RESULTS

### 3.1 | Descriptive statistics

Descriptive statistics are reported in Table 1. The median PBG was 130 mg/dL (equals to 7.2 mmol/L; IQR 49 mg/dL), and the mean PBG was 147 mg/dL (equals to 8.2 mmol/L; SD 62.1 mg/dL). The PBG data correlated strongly with the initial in-hospital serum glucose measurements (Spearman's Rho = 0.701; $P < 0.001$). The median age was 67 years (IQR 25) and 510 (52.6%) patients were male.

Hyperglycemic patients were significantly older and predominantly male, compared to normoglycemic patients. The initial symptoms the patients presented with at first contact with preclinical medical staff did generally not differ between the groups. Only falls ($P = 0.045$) and syncope/orthostatic symptoms ($P = 0.018$) occurred significantly more often in hyperglycemic than in normoglycemic patients. Regarding preclinical vital signs, a significant intergroup difference in oxygen saturation (G1: median 96% [IQR 6.0], G2: median 97% [IQR 4.0]; $P < 0.001$) and heart rate (G1: median 90/min [IQR 40.3], G2 median 86/min [IQR 31.0]; $P = 0.012$) could be detected. Significantly lower sodium (G1: median 139 mmol/L [IQR 4.0], G2: median 140 mmol/L [4.0]; $P < 0.001$) and hemoglobin (G1: median 13.0 g/dL [IQR 2.8], G2: median 13.3 g/dL [IQR 2.3]; $P = 0.002$) levels were detected in hyperglycemic compared to normoglycemic patients. Leukocyte levels were found to be significantly higher in hyperglycemic (median 9.4/$\mu$L [IQR 5.2]) than in normoglycemic patients (median 7.9/$\mu$L [IQR 3.5]; $P < 0.001$). Accordingly, C-reactive protein was significantly higher in hyperglycemic (median 0.6 mg/dL [IQR 2.0]) than in normoglycemic patients (median 0.4 mg/dL [IQR 1.1]; $P < 0.001$). A positive overall correlation of leukocytes and PBG (Spearman's Rho = 0.219; $P < 0.001$), as well as C-reactive protein and PBG (Spearman's Rho = 0.159; $P < 0.001$) could be detected.

In a subgroup analysis depending on the condition of a prediagnosed diabetes, diabetics and non-diabetics were subdivided into 2 groups, using the PBG cutoff of ≥140 mg/dL (Table S1). A significant difference between hyperglycemic and normoglycemic non-diabetics was detected regarding oxygen saturation ($P < 0.001$), heart rate ($P = 0.022$), and systolic blood pressure ($P = 0.027$), whereas there

**TABLE 2** Clinical outcome on hospitalization rate, admission to ICU/IMC, length of stay, and mortality.[a]

| | All patients ($n = 970$) | G1 ($n = 394$) | G2 ($n = 576$) | *P* value | *P* value (ANCOVA) | Odds ratio (95% CI) | Adjusted odds ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| Hospitalization – *n* (% of all patients) | 534 (55%) | 252 (64%) | 282 (49%) | <0.001 | 0.007 | 1.85 (1.42–2.41) | 1.48 (1.11–1.97) |
| Admission–ICU/IMC – *n* (% of all patients) | 389 (40%) | 197 (50%) | 192 (33%) | <0.001 | <0.001 | 2.0 (1.54–2.60) | 1.74 (1.31–2.31) |
| Deceased in hospital – *n* (% of all hospitalized patients) | 47 (4.8%) | 30 (7.6%) | 17 (3.0%) | <0.001 | 0.086 | 2.71 (1.47–4.99) | 1.84 (0.96–3.53) |
| Days in hospital – median (IQR) | 4.0 (7.0) | 6.0 (8.0) | 3.0 (6.0) | <0.001 | <0.001 | n.a. | n.a. |

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; IMC, intermediate care; IQR, interquartile range; n.a., not applicable; PBG, prehospital blood glucose.

[a]G1 (PBG ≥140 mg/dL) and G2 (PBG <140 mg/dL). Multivariable logistic regression models were used–compute adjusted odds ratios and *P* values (ANCOVA) adjusted for age, prediagnosed diabetes, and sex.

were no significant differences in preclinical vital signs between hyper- and normoglycemic diabetics. There was a significant difference in levels of leukocytes ($P < 0.001$) and C-reactive protein ($P = 0.005$) between hyper- and normoglycemic non-diabetics, and there was no difference between hyper- and normoglycemic diabetics. Eleven patients in the non-diabetic hyperglycemic group (4.1%) received the initial diagnosis of diabetes before discharge from the hospital.

## 3.2 | Clinical outcome

The clinical outcome is reported in Table 2. Five hundred thirty-four patients (55%) were hospitalized. Hyperglycemic patients were hospitalized significantly more often compared to normoglycemic patients, with a crude OR of 1.85 (95% CI 1.42–2.41) and an adjusted OR of 1.48 (95% CI 1.11–1.97). A significantly higher admission rate to ICU/IMC was observed in hyperglycemic patients compared to normoglycemic patients, with a crude OR of 2.0 (95% CI 1.54–2.60) and an adjusted OR of 1.74 (95% CI 1.31–2.31). Figure 2 displays the association of PBG and hospitalization rate as well as the corresponding PBG frequency distribution among the patients who were hospitalized. After controlling for age, sex, and prediagnosed diabetes, the observed significant differences in the hospitalization rate ($F$ (4, 965) = 12.64, $P = 0.007$) and in the admission rate to ICU/IMC ($F$ (4, 965) = 11.12, $P < 0.001$) were still significant. Hyperglycemic patients had a longer length of stay in hospital ($P$ <0.001), compared to normoglycemic patients. After controlling for age, sex, and prediagnosed diabetes, this effect was still significant ($F$(4, 965) = 11.43, $P$ <0.001). There was a significant positive overall correlation between PBG and length of stay (Spearman's Rho = 0.237; $P$ <0.001). Compared to normoglycemic patients, hyperglycemic patients were more likely to die in hospital, with a crude OR of 2.71 (95% CI 1.47–4.99) and an adjusted OR of 1.84 (95% CI 0.96–3.53). Figure 3 shows the in-hospital mortality rate and the PBG frequency distribution among the deceased patients. After controlling for age, sex, and prediagnosed diabetes, the difference

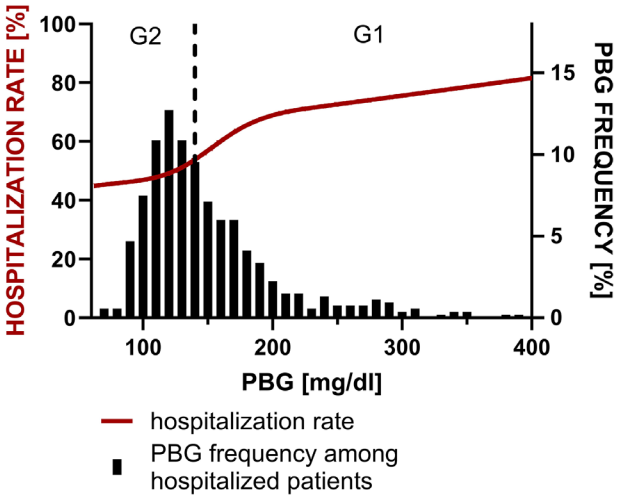


**FIGURE 2** Association between PBG and hospitalization rate. The red line indicates the hospitalization rate (referring to the left *y*-axis). Data are shown in a range of 60–400 mg/dL. The bars indicate the PBG frequency distribution with a bin width of 10 mg/dL among all hospitalized patients ($n = 534$, referring to the right *y*-axis). G1 (PBG ≥140 mg/dL) and G2 (PBG <140 mg/dL). Abbreviation: PBG, prehospital blood glucose.

in the in-hospital mortality rate was not significant anymore ($F$ (4, 965) = 2.96, $P = 0.086$).

Table 3 reports the clinical outcome depending on the condition of a prediagnosed diabetes. Diabetics had a higher hospitalization rate in general (diabetics 69.6%, non-diabetics 52.2%; $P < 0.001$). There was no significant difference between hyperglycemic and normoglycemic diabetics regarding the hospitalization rate ($P = 0.401$), admission to ICU/IMC ($P = 0.292$), length of stay ($P = 0.931$), and in-hospital mortality ($P = 0.378$). In contrast, analyzing patients who were not prediagnosed with diabetes, hyperglycemic non-diabetic patients were more likely to be hospitalized with a crude OR of 1.67 (95% CI 1.24–2.25) and an adjusted OR of 1.49 (95% CI 1.10–2.03) in comparison to normoglycemic non-diabetics. Non-diabetic hyperglycemic patients

**TABLE 3** Clinical outcome on hospitalization rate, admission–ICU/IMC, length of stay, and mortality in diabetic (D) and non-diabetic (ND) patients.[a]

| | All patients ($n = 970$) | Diabetics ($n = 161$) | | | | Non-diabetics ($n = 809$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 ($n = 125$) | D2 ($n = 36$) | *P* value | Odds ratio (95% CI) | Adjusted odds ratio (95% CI) | ND1 ($n = 269$) | ND2 ($n = 540$) | *P* value | *P* value (ANCOVA) | Odds ratio (95% CI) | Adjusted odds ratio (95% CI) |
| Hospitalization – *n* (%) | 534 (55%) | 89 (71%) | 23 (64%) | 0.401 | 1.40 (0.64–3.06) | 1.40 (0.64–3.08) | 163 (61%) | 259 (48%) | <0.001 | 0.010 | 1.67 (1.24–2.25) | 1.49 (1.10–2.03) |
| Admission–ICU/IMC – *n* (%) | 389 (40%) | 68 (54%) | 16 (44%) | 0.292 | 1.49 (0.71–3.14) | 1.49 (0.70–3.17) | 129 (48%) | 176 (33%) | <0.001 | 0.001 | 1.91 (1.41–2.57) | 1.80 (1.32–2.45) |
| Deceased in hospital – *n* (%) | 47 (4.8%) | 13 (10.4%) | 2 (5.5%) | 0.378 | 1.97 (0.42–9.18) | 1.95 (0.42–9.18) | 17 (6.3%) | 15 (2.8%) | 0.015 | 0.117 | 2.36 (1.16–4.80) | 1.80 (0.87–3.72) |
| Days in hospital – median (IQR) | 4.0 (7.0) | 7 (9.0) | 5 (9.5) | 0.931 | n.a. | n.a. | 5 (8.0) | 2 (5.0) | <0.001 | <0.001 | n.a. | n.a. |

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; IMC, intermediate care; IQR, interquartile range; n.a., not applicable; PBG, prehospital blood glucose.
[a]D1 (PBG ≥140 mg/dL), D2 (PBG <140 mg/dL), ND1 (PBG ≥140 mg/dL), and ND2 (PBG <140 mg/dL). Multivariable logistic regression models were used to compute adjusted odds ratios and *P* values (ANCOVA) adjusted for age and sex.

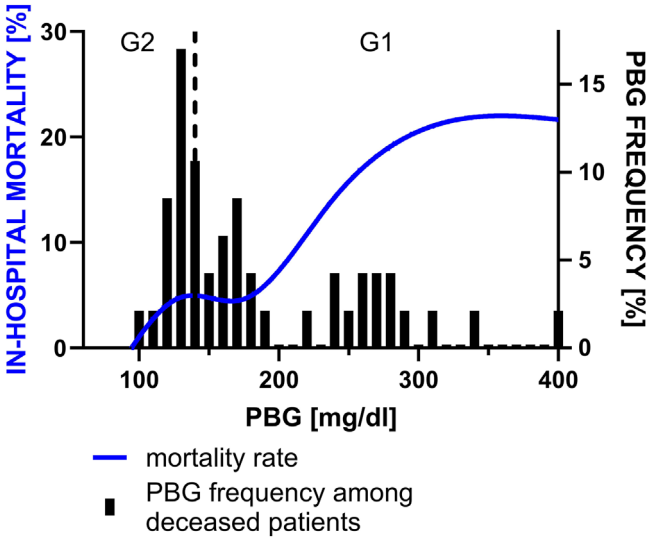


**FIGURE 3** Association between PBG and in-hospital mortality. The blue line indicates the in-hospital mortality (referring to the left *y*-axis). Data are shown in a range of 60–400 mg/dL. The bars indicate the PBG frequency distribution with a bin width of 10 mg/dL among all deceased patients ($n = 47$, referring to the right *y*-axis). G1 (PBG ≥140 mg/dL) and G2 (PBG <140 mg/dL). Abbreviation: PBG, prehospital blood glucose.

were more likely to be admitted to ICU/IMC than normoglycemic non-diabetics with a crude OR of 1.91 (95% CI 1.41–2.57) and an adjusted OR of 1.80 (95% CI 1.32–2.45). Non-diabetic patients with PBG ≥ 140 mg/dL were more likely to die, with a crude OR of 2.36 (95% CI 1.16–4.80) and an adjusted OR of 1.80 (95% CI 0.87 to 3.72), compared to normoglycemic non-diabetics. After controlling the non-diabetic subcohort for age and sex, the differences in the hospitalization rate ($F$ (3, 805) = 6.67, $P = 0.010$) and the ICU/IMC admission rate ($F$ (3, 805) = 14.42, $P = 0.001$) were still significant, but the effect on the in-hospital mortality was not ($F$ (3, 805) = 2.47, $P = 0.117$).

## 4 | LIMITATIONS

This study has several limitations. First, this study reports on only the in-hospital mortality because the study design did not encompass records of patients after discharge from the hospital. Additionally, the number of patients who died in the hospital was small ($n = 47$). Second, no data on glucose-lowering therapies taken by the patients at the time of the study were collected and some of these drugs may have had positive (or negative) effects on the clinical outcome as reported earlier.[26] Third, as no blood sugar records of the diabetic subcohort before submission were available, the differentiation between chronic hyperglycemic states and acute hyperglycemic states (eg, stress hyperglycemia) in these patients is not possible. This aspect would be an interesting approach in further studies. Fourth, correlation analyses of preclinical vital signs (eg, tachycardia, hypoxia, fever, etc.) or clinical data (blood values, ECG, diagnoses, etc.) with PBG were not performed, as many of these data are missing. Last, it has to be mentioned

that the observation period included the first waves of the COVID-19 pandemic.[3,8] This challenging global health crisis caused many changes in society and might have led to a delay in patients seek for medical help, with a possible negative impact on clinical outcomes.[27]

## 5 | DISCUSSION

This study demonstrates an association of prehospital blood glucose measurement and patients' mortality risk. Unlike other studies focusing on elevated blood glucose in the context of trauma,[2] stroke,[9,20,28] acute myocardial infarction[21,22,29] or COVID-19,[3,8] all patients admitted to an internal medicine department by an emergency physician were analyzed in the present study. The median PBG in the analyzed cohort was comparable to previously reported studies.[8,21,30]

A significantly higher hospitalization rate was detected in patients with PBG ≥140 mg/dL compared to patients with lower PBG. Mortality was higher in the hyperglycemic group but this effect was confounded by age, sex, and prediagnosed diabetes. As mortality seems to be stable in the present cohort at a PBG range between 140 and 180 mg/dL, a moderate elevation of PBG (<180 mg/dL) may not be as predictive of worse outcomes than higher PBG levels.[22] Other studies in septic inpatients have shown that the mortality increases especially with very low or very high blood glucose levels.[22,31] The presented results are in concordance with earlier studies, showing elevated blood glucose to be associated with increased length of stay in the hospital, in-hospital complications, and mortality in the setting of general surgery.[4] Therefore, the detection of elevated PBG could be taken into account in the prognosis assessment of patients at risk as exemplified by the proposal to include fasting plasma glucose in the prediction of 90-day mortality in viral pneumonia.[7] Specific diseases in which elevated PBG might be more relevant still need to be determined.

In this study, a significantly higher hospitalization rate and ICU/IMC admission rate could be detected in non-diabetic patients with a PBG ≥140 mg/dL but not in diabetic patients with a PBG ≥140 mg/dL. The effect on the elevated in-hospital mortality rate in non-diabetic patients with PBG ≥140 mg/dL was again confounded by age and sex, as it was not significant anymore after analysis of covariance. It has been reported previously that the association of elevated blood glucose and in-hospital mortality rate is stronger in patients without diabetes compared to diabetics. This effect was shown to be even more pronounced in patients with severe hyperglycemia at hospitalization.[21] In an earlier retrospective analysis of 1886 inpatients, non-diabetic patients with hyperglycemia had an 18.3-times increased mortality, while hyperglycemic patients with prediagnosed diabetes presented with an increase in mortality of only 2.7-times.[32] The present study supports the thesis that elevated blood glucose is more relevant and predictive of the outcome in patients not prediagnosed with diabetes.

An elevated prehospital POCT glucose was shown to be associated with worse neurologic outcome after out-of-hospital cardiac arrest in an earlier study.[33] In the analyzed cohort, a significantly lower proportion of patients presenting with normal frequency sinus rhythm could be detected in patients with PBG ≥140 mg/dL, which at least supports the assumption that arrhythmia may be related to hyperglycemia, which has been described in diabetes before.[34] As inflammation is closely linked to stress hyperglycemia, significantly higher levels of leukocytes and C-reactive protein in patients with elevated blood glucose could be detected, possibly contributing to the aforementioned vicious circle in stress hyperglycemia (Figure 1).

It was shown before that hyperglycemia during ICU admission increases the risk of developing diabetes in the long term.[35] Therefore, all patients with a previously detected hyperglycemic state should be reevaluated on a regular basis to detect the manifestation of diabetes early (eg, by measuring HbA1c every 3–6 months). Although only 4.1% of the non-diabetic, hyperglycemic patients were diagnosed with type 2 diabetes mellitus before discharge from the hospital in the present cohort, a longitudinal study showed that 60% of patients presenting with hyperglycemia on admission are actually diagnosed with diabetes within 1 year.[36] It has to be assumed that many of the patients in the hyperglycemic non-diabetic cohort were already suffering from diabetes mellitus at admission to the hospital.

In emergency medicine, the differentiation between chronic hyperglycemia (as observed in poorly controlled diabetes) or an acute hyperglycemic state (SH) is admittedly challenging. Special attention must be drawn to SH in diabetic patients, as this metabolic state can be diagnosed only from a patient's medical history (especially blood sugar records). The negative consequences of stress hyperglycemia clearly surpass those of chronic hyperglycemia, which may be due to the impossibility to adapt to this metabolic situation on cellular level. It is assumed that insulin-independent glucose transport is not downregulated compensatory in SH, which likely leads to the increase of glucotoxicity.[37] Despite the observed associations with an increased mortality, SH actually might be a necessary adaptation of the organism in case of severe sickness, at least in some acute diseases. To draw the conclusion that a more intensive blood sugar control would improve the patients' outcome would be misleading, as an intensive glucose control in critically ill patients leads to higher mortality than conventional glucose management.[38] This finding is supported by randomized controlled trials that evaluated a tight glycemic control in stroke patients and failed to show that an intensive treatment of elevated blood glucose levels improves mortality.[28,39]

Prehospital POCTof glucose might indicate SH and show an association with patient's admission rate and in-hospital mortality rate. It might therefore contribute to the risk assessment of a patient. As elevated PBG might be more relevant in specific diseases, further studies need to identify specific diagnoses with high relevance of elevated PBG. An elevated PBG might contribute to future scoring systems.

### AUTHOR CONTRIBUTIONS

Peter Kranke, Gülmisal Güder, and Ulrich Dischinge conceptualized the study. Danilo Skudelny performed data curation. Simon Kloock, Danilo Skudelny, and Ulrich Dischinge did formal analysis. Simon Kloock drafted the original manuscript and was responsible for the visualization, and all authors contributed substantially to its revision. Ulrich Dischinge supervised the whole process and takes responsibility for the paper as a whole.

## ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

## CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

## ORCID

*Ulrich Dischinger MD, PhD* https://orcid.org/0009-0008-4885-9355

## REFERENCES

1. Farrugia Y, Mangion J, Fava M-C, Vella C, Gruppetta M. Inpatient hyperglycaemia, and impact on morbidity, mortality and re-hospitalisation rates. *Clin Med (Lond)*. 2022;22(4):325-331.
2. Kreutziger J, Lederer W, Schmid S, et al. Blood glucose concentrations in prehospital trauma patients with traumatic shock: a retrospective analysis. *Eur J Anaesthesiol*. 2018;35(1):33-42.
3. Wu J, Huang J, Zhu G, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. *BMJ Open Diabetes Res Care*. 2020;8:e001476.
4. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care*. 2010;33(8):1783-1788.
5. Ishihara M. Acute hyperglycemia in patients with acute myocardial infarction. *Circ J*. 2012;76(3):563-571.
6. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response!. *Crit Care*. 2013;17(2):305.
7. Xu J, Zhao J, Wu L, Lu X, et al. Fasting plasma glucose levels at the time of admission predict 90-day mortality in patients with viral pneumonia. a prospective study. *Exp Clin Endocrinol Diabetes*. 2023;131(5):290-298.
8. Fehlmann CA, Suppan L, Gaudet-Blavignac C, Elia N, Gariani K. Association between prehospital blood glucose levels and outcomes in patients with COVID-19 infection: a retrospective cohort study. *Exp Clin Endocrinol Diabetes*. 2023;131(6):338-344.
9. Vibo R, Korv J, Roose M. One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from Tartu, Estonia. *Eur J Neurol*. 2007;14(4):435-439.
10. Kesavadev J, Misra A, Saboo B, et al. Blood glucose levels should be considered as a new vital sign indicative of prognosis during hospitalization. *Diabetes Metab Syndr*. 2021;15(1):221-227.
11. Harbuz MS, Lightman SL. Stress and the hypothalamo-pituitary-adrenal axis: acute, chronic and immunological activation. *J Endocrinol*. 1992;134(3):327-339.
12. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332(20):1351-1362.
13. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation*. 2002;106(16):2067-2072.
14. Piarulli F, Sartore G, Sechi A, et al. Low glucose concentrations induce a similar inflammatory response in monocytes from type 2 diabetic patients and healthy subjects. *Oxid Med Cell Longev*. 2017;2017:9185272.
15. Stegenga ME, Crabben S, Dessing MC, et al. Effect of acute hyperglycaemia and/or hyperinsulinaemia on proinflammatory gene expression, cytokine production and neutrophil function in humans. *Diabet Med*. 2008;25(2):157-164.
16. Alexiewicz JM, Kumar D, Smogorzewski M, Klin M, Massry SG. Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. *Ann Intern Med*. 1995;123(12):919-924.
17. Delamaire M, Maugendre D, Moreno M, Le Goff M-C, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. *Diabet Med*. 1997;14(1):29-34.
18. Boden G, Vaidyula VR, Homko C, Cheung P, Rao AK. Circulating tissue factor procoagulant activity and thrombin generation in patients with type 2 diabetes: effects of insulin and glucose. *J Clin Endocrinol Metab*. 2007;92(11):4352-4358.
19. Stegenga ME, Van Der Crabben SN, Blümer RME, et al. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. *Blood*. 2008;112(1):82-89.
20. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet*. 2009;373(9677):1798-1807.
21. Ishihara M, Kojima S, Sakamoto T, et al. Comparison of blood glucose values on admission for acute myocardial infarction in patients with versus without diabetes mellitus. *Am J Cardiol*. 2009;104(6):769-774.
22. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355(9206):773-778.
23. American Diabetes Association Professional Practice, C., 16. Diabetes care in the hospital: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S244-S253.
24. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(1):16-38.
25. Bogun M, Inzucchi SE. Inpatient management of diabetes and hyperglycemia. *Clin Ther*. 2013;35(5):724-733.
26. Zhu Z, Zeng Q, Liu Q, Wen J, Chen G. Association of glucose-lowering drugs with outcomes in patients with diabetes before hospitalization for COVID-19: a systematic review and network meta-analysis. *JAMA Netw Open*. 2022;5(12):e2244652.
27. Gertz AH, Pollack CC, Schultheiss MD, Brownstein JS. Delayed medical care and underlying health in the United States during the COVID-19 pandemic: a cross-sectional study. *Prev Med Rep*. 2022;28:101882.
28. Johnston KC, Bruno A, Pauls Qi, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. *JAMA*. 2019;322(4):326-335.
29. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005;111(23):3078-3086.
30. Sardu C, D'onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care*. 2020;43(7):1408-1415.
31. Wei X, Min Yu, Yu J, et al. Admission blood glucose is associated with the 30-days mortality in septic patients: a retrospective cohort study. *Front Med (Lausanne)*. 2021;8:757061.
32. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87(3):978-982.
33. Abramson TM, Bosson N, Whitfield D, Gausche-Hill M, Niemann JT. Elevated prehospital point-of-care glucose is associated with worse neurologic outcome after out-of-hospital cardiac arrest. *Resusc Plus*. 2022;9:100204.
34. Grisanti LA. Diabetes and arrhythmias: pathophysiology, mechanisms and therapeutic outcomes. *Front Physiol*. 2018;9:1669.
35. Ali Abdelhamid Y, Kar P, Finnis ME, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Crit Care*. 2016;20(1):301.

36. Greci LS, Kailasam M, Malkani S, et al. Utility of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. *Diabetes Care*. 2003;26(4):1064-1068.
37. Scheen M, Giraud R, Bendjelid K. Stress hyperglycemia, cardiac glucotoxicity, and critically ill patient outcomes current clinical and pathophysiological evidence. *Physiol Rep*. 2021;9(2):e14713.
38. Investigators N-SS, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
39. Long B, Koyfman A, Gottlieb M. Effect of tight glycemic control on patients with ischemic stroke. *Acad Emerg Med*. 2021;28(2):255-257.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Kloock S, Skudelny D, Kranke P, et al. Association of preclinical blood glucose with hospitalization rate and in-hospital mortality: A single-center retrospective cohort study. *JACEP Open*. 2024;5:e13091. https://doi.org/10.1002/emp2.13091

## AUTHOR BIOGRAPHY

**Simon Kloock**, MD, is a doctor in training in the Department of Internal Medicine, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany.